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## EXPERIENCE WITH INFECTIOUS HEPATITIS AT ROYAL PRINCE ALFRED HOSPITAL.

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CONTINUOUS interest in infectious hepatitis since the early years of the recent World War has led to major advances in our understanding of this malady. The stimulus was the increased incidence in service personnel in all armies engaged in the European, Mediterranean and South-East Asian battle areas. As the war years advanced, outbreaks occurred in civilian populations, notably in the Scandinavian countries and in particular Denmark, where Alsted (1947) reported an outbreak with high fatality and morbidity in the older age group and female sex.

The main worry to the services was not the mortality, which was strikingly low, but the loss of active manpower often at critical times. One remembers the many cases among servicemen in the Middle East and in particular in the Tobruk fortress, where the incidence fell most heavily on the officer population. In the Australian Imperial Force in the Middle East the rate per 1000 rose from 1·89 in 1940 to 14·74 in 1941 and 33·9 in 1942. The highest Australian Imperial Force incidence in the South-West Pacific Area was 9·25 per 1000 in 1944. In contrast, the rate of incidence of the disease per 1000 in the Australian Military Forces personnel in Australia was 0·15 in 1942, 1·81 in 1943, 0·63 in 1944 and 0·56 in 1945. These figures show the importance of infectious hepatitis in our forces in the Middle East where the disease was endemic, in contrast with Australia where the incidence was low. No satisfactory service figures are available for the incidence of hepatic necrosis and chronic hepatitis, but it would appear that these complications were few in number.

The theory and viewpoint of Virchow (1864) that this form of jaundice was due to catarrhal changes in the duodenum—the so-called "catarrhal jaundice"—persisted up to the late thirties of this century. Eppinger pointed out during the first World War that these catarrhal changes were not seen in post-mortem studies on subjects who had died of the disease. Gradually the evidence was collected that this disease was in fact a diffuse hepatitis (Figure I); but this concept was tardily accepted. Notable contributions to the pathology of infectious hepatitis included Lucké's (1944) painstaking post-mortem findings on 125 American servicemen who had died from this disease, and later another excellent paper by Lucké and Mallory (1946) on the acute fulminating type. Acceptance of these facts was accelerated by Iverson and Roholm (1939), who as early as 1935 described a technique for aspiration hepatic biopsy. They reported studies based on 38 aspiration biopsies. This technique has now been universally accepted and is widely practised all over the world. It has evoked studies on "living" histopathology and the correlation of histological and biochemical studies such as that of Dible, McMichael and Sherlock (1943).

The "virus" of infectious hepatitis has not so far been transmissible to experimental animals, and the case for an infection rests mainly on transmission experiments on human volunteers described by Cameron (1943) and by MacCallum and Bradley (1944) in England.

The clinical diagnosis of infectious hepatitis has been greatly assisted by the evolution of the various flocculation tests, which usually produce strikingly positive results in hepatocellular disease. The first described was the Takata-Ara test, which served as a stimulus to many workers to discover tests more specific for hepatocellular disease. Hanger (1939) described the cephalin cholesterol flocculation test, Gray (1940) the colloidal gold test, and MacLagan (1944) the thymol turbidity test. Since then many other tests and modifications of those mentioned have been introduced.

Many analyses of the clinical manifestations of infectious hepatitis have been made in detail in the literature, notably that of Havens (1948), and the symptomatology is well known. It has been estimated, however, that for every jaundiced patient with infectious hepatitis there are three to six non-jaundiced persons suffering from the disease. It is possible that a proportion of the patients with cirrhosis stem from this unjaundiced group, but this is purely speculative. Certain modes of presentation may cause confusion in the differential diagnosis, and those mentioned in the present series of cases will be discussed.

This paper describes the experience with 83 patients suffering from disease admitted to the Royal Prince Alfred Hospital between June, 1949, and November, 1951, and covers all patients admitted to hospital with infectious hepatitis over a period of twenty-nine months. Either these patients were directly in the care of the gastro-enterological unit of the hospital, or else the members of the unit were given permission to see them and follow their progress. Considerable care has been taken to make a correct diagnosis of infectious hepatitis and to eliminate the possibility of serum hepatatis, infective mononucleosis or other diseases. One realizes to the full the difficulty of making a certain diagnosis even in the presence of the expected biochemical and histopathological findings, as in this disease there is no specific test and facilities for the demonstration of the virus were not available to us.

The two most important aspects of this disease are, firstly, the tendency for some patients to progress to chronic hepatitis and hepatic cirrhosis, and secondly, the occasional sudden development of acute hepatic necrosis, which may occur initially or at any stage of the disease.

## Analysis of Cases of Infectious Hepatitis at the Royal Prince Alfred Hospital between June, 1949, and November, 1951.

An analysis of those cases in which the diagnosis of infectious hepatitis was made, at the Royal Prince Alfred Hospital between June, 1949, and November, 1951, is presented in the following section and in Table I. There were 83 admissions with a female to male predominance of almost two to one (females 64·7%, males 35·3%). Of these 69 patients or 83·2% appeared to make a complete recovery, in four or 4·8% complete recovery is still doubtful as yet, seven or 8·4% have progressed to a state of chronic hepatitis with the disease process still "active". The ages of the patients were as follows: up to ten years, 14; eleven to twenty years, 21; twenty-one to thirty years, 29; thirty-one to forty years, 11; forty-one to fifty years, five; fifty-one to sixty years, three; over sixty years, none. A comparison of these figures of progressive hepatitis with published data is given in Table II.

Three patients (3·6%) died, one in the acute stage, one with chronic hepatitis followed by necrosis, and one from hæmatemesis in the chronic progressive stage.

Four patients were pregnant, the infection occurring in the sixth month in three cases and in the first three months in the fourth (Case 3). Two have apparently fully recovered, the condition of the third is still doubtful but full recovery is probable, the fourth progressed to chronic hepatitis. All were delivered of normal full-term infants.

The age incidence followed the usual pattern and the accepted view that the disease is mainly seen in youth. Of the patients, 80% were aged under thirty-one years, and there were no patients aged over sixty years.

### Problems in Diagnosis.

In most instances the diagnosis of infectious hepatitis is straightforward. The onset is usually insidious with anorexia, nausea, lassitude, disinclination for effort, malaise and weakness. Within a few days abdominal discomfort accompanied by jaundice and mild pyrexia occurs. However, in many instances the diagnosis is more obscure, particularly in the non-icteric cases and in those in which certain single symptoms are greatly magnified. The following will be discussed briefly: (*a*) diarrhœa as an initial symptom, (*b*) joint pains and swellings, (*c*) neurological symptoms and mental states, (*d*) hæmorrhagic states and (*e*) pain.

#### *Diarrhœa as an Initial Symptom.*

As there is reason to believe that infectious hepatitis is a generalized systemic infection in which the alimentary canal is involved early, it is not surprising that in many cases it commences with diarrhœa. An initial diagnosis of gastro-enteritis is often made. Striking examples in this series were Cases 1, 4, 31, 35, 40 and 49. In two other instances diarrhœa was an early and transient symptom.

In a survey of the early symptoms of 156 patients suffering from infectious hepatitis, Sborov and Keller (1951) report 5% complaining of diarrhœa. In our series the incidence was 10%, and we regard diarrhœa as a common symptom of this disease.

Table I.

| Series. | Number of Cases. | Number of Cases of Progressive Hepatitis. |
|---|---|---|
| Royal Prince Alfred Hospital figures .. | 83 | 7 |
| Dible *et alii* (1943) .. .. .. | 54 | 3 |
| Sherlock and Walshe (1946) .. .. | 35 | 0 |
| Mallory (1947) .. .. .. .. | 89 | 0 |
| Koek (1947) .. .. .. .. | 400 | 12 |

#### *Joint Pains and Swellings.*

Rennie (1945), in Glasgow, in a review of 39 cases of infectious hepatitis found in eight the complaint of joint pains. In our series one patient (Case 1) complained initially of joint pains, another (Case 4) presented initially with pains in joints which lasted a week, and yet another (Case 26) gave a history eight weeks before admission to hospital of boring pains in all limb joints, especially the wrists, and in the neck, and aggravated by movement.

#### *Neurological Complications.*

One gathers from the literature that neurological symptoms are not commonly found in infectious hepatitis. There has also been doubt as to whether in such cases when neurological signs were gross two diseases existed at the same time. It is now generally accepted that the virus of infectious hepatitis can cause inflammatory changes in the central nervous system.

In our series of cases, only one patient presented with a definite neurological picture, but it was of a dramatic nature.

Case 60.—A male patient, aged twenty-six years, was admitted to the Royal Prince Alfred Hospital on April 21, 1950. Two weeks beforehand he had become listless and tired and had a headache, but continued to go to work. One day before his admission to hospital he came home feeling nauseated. His mother arrived home later, found him apparently asleep on the sofa and could not rouse him. When his doctor arrived he was found to be making athetoid movements of both hands and arms and his pupils were widely dilated and did not react to light. Later his temperature rose to 101° F. and he became deeply comatose. For the past eighteen hours he had been completely unconscious and had had several rigors and vomited copiously. A few purpuric spots on the lower aspect of the left side of the chest were noticed. His neck became stiff and he had retention of urine.

He was admitted to the Royal Prince Alfred Hospital at 4 p.m. on April 21, deeply comatose, with a temperature of 101° F., pupils dilated and inactive and eyeballs moving about continuously. His jaws tightened and relaxed spasmodically. Neck rigidity was present. There were

athetoid movements of the upper limbs and muscle tone changes, sometimes rigid, sometimes flaccid. The tendon reflexes were normal. Later, coarse writhing movements of both lower limbs were noted. The plantar reflexes were flexor type. There was no papilloedema. The liver and spleen were not palpable.

Three days later he was fully conscious and developed the usual clinical picture of hepatocellular jaundice with positive biochemical and aspiration liver biopsy findings.

*Mental States.*—Many patients presented with initial symptoms of weariness, listlessness, disinclination for effort or disturbances of consciousness. For example, in Case 30 the patient, a child, aged five years, woke up four days before admission to hospital, tired and listless, and became delirious and irrational. When first examined in hospital she was hard to rouse and made no attempt to speak or cry. In Table I numerous patients are listed who had mental apathy, languor or intense mental weariness. Such symptoms we have attributed to the toxic effects of hepatocellular damage.

A striking example is that of the patient in Case 73, a male, aged thirty-five years, who was admitted to hospital with a history of anorexia, nausea and vomiting commencing seven days beforehand. For the last three or four days he had suffered severe epigastric pain and jaundice. He continued to go to work, but his condition deteriorated and he was admitted to hospital semiconscious and delirious. On examination he was delirious, lethargic, dehydrated and jaundiced. His liver was palpable and tender four fingers' breadth below the costal margin, and his spleen was just palpable. With intravenous glucose and serum therapy he quickly recovered his normal mental state.

If we wish to reduce the incidence of hepatic necrosis and progressive hepatitis, careful watch must be kept on patients presenting with these symptoms. We have found that a disinclination for effort in one usually active and bright is an important indication of hepatic cell damage.

*Bleeding Episodes.*

In an extensive review of the literature of infectious hepatitis, W. Paul Havens (1948) does not mention the occurrence of bleeding episodes in this disease.

In Rennie's (1945) careful analysis of 39 cases of infectious hepatitis, two patients exhibited a hæmorrhagic tendency. Stefanini and Petrillo (1949) studied 30 patients with hepatic disease which was associated with a hæmorrhagic tendency and found the prothrombin index below 50% in eight and below 25% in seven, while in the remainder altered capillary fragility alone appeared responsible for hæmorrhagic manifestations. They suggest that hypoprothrombinæmia and increased capillary fragility are the factors which may have a common underlying mechanism such as deficient utilization of vitamin *K* by the diseased liver.

Whitesell and Snell (1949) described 41 cases of hepatitis or cirrhosis, in 37 of which there was thrombocytopenia or increased fragility or both. As these cases are described, one is not sure how many of the patients were suffering from acute infectious hepatitis.

Traisman, Wheeler and Fager (1950) described three cases of virus hepatitis in infancy, and in one of these there was a thrombocytopenia of 30,000 per cubic millimetre.

It would thus appear that in acute infectious hepatitis the bleeding phenomena are associated with either hypoprothrombinæmia or thrombocytopenia.

In our series of cases of infectious hepatitis eleven patients had hæmorrhagic phenomena of some degree, and in five of these bleeding dominated the picture.

In Case 62 hæmorrhagic phenomena were prominent and included epistaxis, spontaneous bleeding into the lips and gums, hæmatemesis and malæna. The prothrombin index was greatly reduced, but red cell fragility was normal.

In Case 77 a male patient, aged eight years, was admitted to hospital with a diagnosis of acute glomerulonephritis (Ellis Type I), his main symptom being hæmaturia. It soon became evident that he was suffering from infectious hepatitis.

In Case 79 a male patient, aged forty-four years, presented with hæmatemesis and melæna, petechial hæmorrhages into the skin and epistaxis. The prothrombin index was normal and red cell fragility increased, but the initial platelet count was low.

These patients have been fully described by Billington (1952).

*Pain.*

Most patients suffering from infectious hepatitis complain of a sense of tightness or a dragging sensation in the right upper quadrant of the epigastrium. It is recorded that exploratory laparotomy has been performed for suspected acute abdominal emergencies such as appendicitis and cholecystitis.

Two of the patients in this series (Cases 30 and 48) suffered severe pain which led to laparotomy, whilst several others had pain of much greater degree of severity than is usually encountered in this disease. The origin of the pain is believed to be sudden hepatic enlargement and stretching of the capsule.

### The Problem of Infectious Hepatitis Occurring in the Course of Pregnancy.

In this series there were four patients who developed infectious hepatitis in pregnancy, three in the sixth month of pregnancy, and one in the first trimester (Cases 3, 49, 53 and 54). Two of these responded well to treatment, the third result is in doubt, and one patient progressed to chronic hepatitis. All the patients came to term without further trouble and had normal full-time babies. There was no maternal mortality.

The incidence of infectious hepatitis in pregnancy is variable, depending upon the incidence in the general population. As in this series the largest number of cases occurred in the age period twenty-one to thirty years, the practical importance of this disease to the physician and obstetrician is obvious. Nevertheless Mickel (1951), reviewing the cases of infectious hepatitis occurring at the Charity Hospital of New Orleans from 1940 to 1949, could find only fifteen cases in 69,186 deliveries, an incidence of 0·022%.

In our series there was no mortality in pregnancy and no fœtal mortality. Mickel reported a high mortality rate of 13·6% in pregnant women, while Zondek and Bromberg's mortality figures were 17·2% in 29 cases.

Lichtman dissociates hepatitis in pregnancy from obstetric acute yellow atrophy, and considers that the danger of maternal death from hepatitis is small.

In the light of our knowledge of the prognosis in infectious hepatitis generally it would seem that pregnancy offers an additional burden in coping with this infection, and that treatment should be even more carefully undertaken in the pregnant woman. There would appear to be an increased liability to hepatic necrosis, and the cases of acute yellow atrophy occurring during the course of pregnancy may be examples of an acute fulminating virus disease. One of our patients progressed to hepatic cirrhosis. This complication occurring in a young mother is sufficiently serious to warrant constant care in the supervision of the pregnant woman who becomes jaundiced. One would emphasize the importance of adequate and perhaps prolonged rest until all symptoms and signs of the disease have disappeared and the results of biochemical investigations have returned to full normality.

### The Problem of Progressive Hepatitis.

Our unit has been perturbed by the increasing number of patients with progressive hepatitis admitted to the hospital, and has given much thought to ætiological factors and methods of treatment and followed the literature closely in the hope that some light will be shed on this problem. Unfortunately no cure has yet appeared. In our series one has been interested by the varying rate of progress of this disease and by its different clinical manifestations. Can one divide these cases into two groups? In one group the emphasis will be on jaundice which persists for many months with but mild clinical symptoms. In the second the emphasis is on ascites and œdema of the ankles, lowered serum albumin and high serum globulin figures and reversed albumin-globulin ratio. In these two types the histological findings may be identical. One is tempted to think that in the former type of case there is

TABLE II.

*Infective Hepatitis: June, 1949, to November, 1951*

| Case No. | Age. (Years.) | Sex. | Symptoms and Signs. | | | | | | | Biochemical Findings (on Admission to Hospital). | | | | | Liver Biopsy Findings. | Remarks | Result. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nausea. | Abdominal Pain. | Anorexia. | Jaundice. | Liver Size.[1] | Bleeding. | Mental Condition. | Serum Bilirubin Content.[2] | Alkaline Phosphatase Content.[3] | Thymol Flocculation Test. | Prothrombin Index. | Total Serum Protein Content.[4] | | | |
| 1 | 33 | M. | + | + | + | +++ | 2F. | – | – | 9·5 | 19·5 | – | 80 | 7·45 | Changes suggestive of recurring infective hepatitis with some evidence of fibrosis. | | Doubtful. |
| 2 | 57 | F. | +++ | ++ | ++++ | – | 4F. | – | – | 0·4 | 11·4 | ++++ | 68 | 5·9 | Progressive hepatitis going on to cirrhosis. | Progressive hepatitis. | Unrelieved. |
| 3 | 31 | F. | + | + | + | Slight. | 1F. | ++++ | – | 1·33 | 17·8 | ++++ | 95 | 8·2 | Progressive hepatitis. | Progressive hepatitis. | Unrelieved. |
| 4 | 25 | F. | ++ | – | + | ++ | — | – | Normal. | 4·25 | 26·0 | ++++ | 75 | 8·5 | Active progressive hepatitis. | Progressive to cirrhosis. | Unrelieved. |
| 5 | 40 | M. | +++ | – | ++ | – | — | – | – | Not estimated. | Not estimated. | Not performed. | Not estimated. | Not estimated | Hepatic necrosis. | | Died. |
| 6 | 23 | F. | ++ | + | ++ | ++ | 1F. | — | – | 15·5 | 32·4 | ++++ | 97 | 6·3 | (i) Acute hepatitis. (ii) Recovery. | Good response to prolonged medical treatment. | Relieved. |
| 7 | 5 | M. | ++ | ++ | + | +++ | 1F. | — | Restless, drowsy. | 6·0 | 39·6 | ++++ | 77 | 7·45 | Resolving hepatitis. | Good response to therapy. | Relieved. |
| 8 | 7 | F. | ++ | – | ++ | ++ | 1F. | — | Quiet. | 5·0 | 22·2 | ++++ | | 7·1 | Nil. | Good response to therapy. | Relieved. |
| 9 | 10 | F. | ++ | + | ++ | + | 1F. | — | Apathetic. | 4·2 | 16·8 | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 10 | 46 | F. | +++ | ++ | ++ | ++ | — | — | Drowsy. | 9·0 | 29·1 | ++++ | 64 | 7·1 | Nil. | Good response to therapy. | Relieved. |
| 11 | 20 | F. | ++ | ++ | + | — | 1F. | — | Weary, depressed. | <0·2 | | ++++ | | | Nil. | Second attack in one year—good clinical response. | Relieved. |
| 12 | 39 | F. | +++ | + | +++ | ++ | — | ++ | Lethargic. | 12·5 | 54·0 | ++++ | | 8·6 | Nil. | Good clinical response to prolonged bed rest. | Relieved. |
| 13 | 18 | F. | +++ | — | ++ | + | — | — | — | 2·0 | | ++ | | | Nil. | Good clinical response to prolonged bed rest. | Relieved. |
| 14 | 27 | M. | ++ | — | ++ | +++ | 1F. | — | Lethargic. | 23·5 | 22·8 | ++++ | 94 | | Nil. | Good clinical response to prolonged rest. | Relieved. |
| 15 | 20 | F. | ++ | — | ++ | ++ | 1F. | — | Lethargic. | 6·0 | 12·3 | ++++ | | | Nil. | Good clinical response. | Relieved. |
| 16 | 10 | F. | ++ | + | ++ | ++ | 1F. | — | Listless. | 11·5 | 25·5 | ++++ | | 8·05 | Nil. | Good clinical response. | Relieved. |
| 17 | 14 | F. | +++ | — | +++ | — | — | — | — | 4·5 | 17·7 | ++++ | | 6·9 | Nil. | Good response to treatment. | Relieved. |
| 18 | 18 | F. | +++ | ++ | +++ | ++ | 1F. | — | Lethargic. | 8·25 | 10·2 | ++++ | | | Nil. | Good clinical response. | Relieved. |
| 19 | 22 | F. | +++ | + | +++ | + | 1F. | — | Lethargic. | 5·4 | 14·4 | ++++ | 68 | | Nil. | Good clinical response. | Relieved. |
| 20 | 19 | F. | ++ | ++ | ++ | + | 1F. | – | Tired. | 2·0 | 30·0 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 21 | 14 | F. | ++ | + | +++ | +++ | 1F. | — | Lethargic. | 4·5 | 34·8 | ++++ | | 8·25 | Nil. | Good response to treatment. | Relieved. |
| 22 | 37 | M. | ++ | ++ | + | ++++ | 3F. | — | Lethargic. | 19·0 | 18·6 | ++++ | | 7·2 | Nil. | Good response to prolonged rest in bed. | Relieved. |
| 23 | 10 | F. | ++ | ++ | ++ | + | 1F. | — | Lethargic. | 2·0 | 36·0 | ++++ | | 7·4 | Nil. | Good response to treatment. | Relieved. |
| 24 | 11 | F. | +++ | + | ++ | + | 1F. | — | Apathetic. | 8·7 | 37·0 | ++++ | | 7·1 | Nil. | Good response to treatment. | Relieved. |
| 25 | 27 | F. | + | + | ++ | – | 1F. | — | — | 0·4 | 7·8 | +++ | | 7·1 | Recovering hepatitis. | Good clinical response. | Relieved. |
| 26 | 29 | F. | ++ | ++ | ++ | ++ | 4F. | ++ | — | 15·4 | 20·4 | Negative | 46 | 6·7 | Nil. | Good response to therapy. | Relieved. |
| 27 | 11 | F. | +++ | + | ++ | ++ | 1F. | – | Lethargic. | 8·1 | 25·8 | ++++ | | 7·85 | Nil. | Good response to therapy. | Relieved. |
| 28 | 21 | M. | ++ | – | ++ | ++ | 3F. | – | Apathetic. | 13·5 | 21·0 | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 29 | 29 | M. | ++ | + | ++ | + | 1F. | – | — | 3·7 | | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 30 | 5 | F. | ++++ | ++ | ++ | ++ | 1F. | – | Delerious for four days. | 6·5 | 16·5 | ++++ | | 6·1 | Nil. | Good response to treatment. | Relieved. |
| 31 | 8 | M. | ++++ | + | ++++ | ++ | 5F. | – | — | 4·7 | 21·0 | ++++ | 100 | | Nil. | Good response to therapy. | Relieved. |
| 32 | 21 | M. | ++ | +++ | ++ | ++ | 3F. | ++++ | — | 7·5 | 20·4 | +++ | 85 | 7·1 | Recovering hepatitis. | Responded well to therapy. | Relieved. |
| 33 | 20 | F. | ++ | + | ++ | + | 2F. | – | — | 5·5 | 27·0 | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 34 | 7 | M. | ++ | + | ++ | + | 1F. | – | — | 2·0 | 26·4 | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 35 | 29 | F. | + | + | ++ | ++ | 1F. | – | — | 5·5 | | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 36 | 21 | M. | + | +++ | ++ | ++ | — | – | — | 12·5 | 11·1 | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 37 | 21 | F. | +++ | + | ++++ | ++ | — | – | Apathetic, had headache. | 5·0 | | ++++ | | | Nil. | Good response to therapy. | Relieved. |
| 38 | 8 | F. | ++ | – | ++ | ++ | 1F. | – | — | 4·0 | 11·1 | ++++ | | 7·45 | Nil. | Good response to therapy. | Relieved. |
| 39 | 20 | F. | +++ | ++ | ++ | – | — | – | — | 0·2 | | ++ | | | Nil. | Good response to therapy. | Relieved. |
| 40 | 29 | M. | +++ | – | ++++ | – | — | – | — | 0·2 | 4·8 | ++++ | | | Resolving hepatitis. | Good response to prolonged bed rest. | Relieved. |
| 41 | 40 | F. | +++ | + | ++++ | + | 1F. | – | — | 3·6 | 22·5 | ++++ | | 5·9 | Nil. | Good response to prolonged bed rest. | Relieved. |

[1] Fingers' breadth below the costal margin. [2] Milligrammes *per centum* [3] King-Armstrong units. [4] Grammes *per centum*.

TABLE II.—*Continued.*

*Infective Hepatitis: June, 1949, to November, 1951.*—Continued.

| Case No. | Age. (Years.) | Sex. | Symptoms and Signs. | | | | | | | Biochemical Findings (on Admission to Hospital). | | | | | Liver Biopsy Findings. | Remarks. | Result. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nausea. | Abdominal Pain. | Anorexia. | Jaundice. | Liver Size.[1] | Bleeding. | Mental Condition. | Serum Bilirubin Content.[2] | Alkaline Phosphatase Content.[3] | Thymol Flocculation Test. | Prothrombin Index. | Total Serum Protein Content.[4] | | | |
| 42 | 19 | M. | +++ | + | +++ | ++ | 2F. | – | — | 12·0 | 12·6 | ++++ | 84 | 7·85 | Nil. | Good response to prolonged bed rest. | Relieved. |
| 43 | 31 | F. | ++ | + | ++ | + | 1F. | – | — | 2·5 | | ++++ | | | Resolving hepatitis. | Good response to prolonged bed rest. | Relieved. |
| 44 | 10 | M. | ++++ | +++ | ++++ | ++ | 1F. | ++ | — | 7·0 | 27·0 | ++++ | | | Nil. | Good response to prolonged bed rest. | Relieved. |
| 45 | 54 | M. | +++ | + | +++ | ++ | 1F. | – | — | 9·5 | 36·3 | ++++ | | | Nil. | Good response to prolonged bed rest. | Relieved. |
| 46 | 23 | M. | +++ | + | +++ | ++ | 2F. | – | — | 4·0 | 19·2 | ++++ | | | Nil. | Good response to prolonged bed rest. | Relieved. |
| 47 | 21 | M. | ++++ | ++ | +++ | + | 1F. | – | — | 2·5 | 6·8 | ++++ | 86 | | Resolving hepatitis. | Good response to prolonged bed rest. | Relieved. |
| 48 | 11 | F. | ++ | ++++ | ++ | ++ | 2F. | – | — | 9·5 | 19·6 | ++++ | | | Nil. | Operation — appendicectomy. Good response to prolonged bed rest. | Relieved. |
| 49 | 24 | F. | ++++ | + | ++++ | +++ | 1F. | – | — | 14·0 | 18·3 | ++++ | 74 | 4·7 | Nil. | Six months pregnant. Baby normal (full term). | Doubtful. |
| 50 | 21 | M. | ++ | +++ | – | – | — | – | — | 4·0 | 18·0 | ++++ | | 7·1 | Nil. | Good response to therapy. | Relieved. |
| 51 | 56 | F. | +++ | – | +++ | +++ | 2F. | – | — | 10·0 | 14·1 | ++++ | | 6·7 | Progressive hepatitis going on to cirrhosis. | Hæmolysis +++—operation—splenectomy. | Unrelieved. |
| 52 | 42 | M. | ++ | ++ | +++ | ++ | — | – | — | 10·0 | 4·8 | ++++ | 75 | 5·5 | Progressive hepatitis. | Progressive hepatitis. | Unrelieved. |
| 53 | 23 | F. | +++ | +++ | +++ | ++ | — | – | — | 8·5 | 24·3 | ++++ | 73 | | Nil. | Six months pregnant. Baby normal (full term). Good response to treatment. | Relieved. |
| 54 | 21 | F. | ++ | – | ++ | ++ | – | – | — | 8·5 | 16·5 | +++ | | 7·5 | Nil. | Six months pregnant. Baby normal (full term). Good response to treatment. | Relieved. |
| 55 | 38 | M. | +++ | + | +++ | +++ | 3F. | – | — | 27·0 | 30·0 | +++ | 75 | | Nil. | Good response to treatment. | Relieved. |
| 56 | 11 | M. | +++ | +++ | +++ | ++ | 1F. | – | — | 10·0 | 28·2 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 57 | 8 | F. | ++ | – | ++ | ++ | 1F. | – | — | 6·0 | 10·2 | +++ | | | Nil. | Good response to treatment. | Relieved. |
| 58 | 40 | F. | +++ | + | +++ | +++ | 2F. | – | — | 8·5 | 18·6 | ++ | 78 | | Resolving hepatitis. | Operation—laparotomy and liver biopsy. | Doubtful. |
| 59 | 24 | F. | ++++ | – | ++++ | + | 1F. | – | Apathetic. | 0·8 | 9·3 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 60 | 26 | M. | +++ | – | ++ | – | 1F. | – | Deeply comatose. | 13·5 | 11·1 | ++++ | | 5·9 | Resolving hepatitis. | Good response to treatment. | Relieved. |
| 61 | 46 | F. | +++ | ++ | +++ | – | 1F. | – | — | 27·0 | 18·0 | +++ | | 6·6 | Nil. | Good response to treatment. | Relieved. |
| 62 | 16 | F. | + | – | + | ++ | — | ++++ | — | 10·0 | 6·9 | ++++ | 10 | 9·6 | Progressive hepatitis. | Progressive hepatitis. | Unrelieved. |
| 63 | 24 | F. | + | + | + | + | 2F. | – | — | 8·0 | 25·8 | +++ | | | Nil. | Good response to treatment. | Relieved. |
| 64 | 5 | M. | ++ | + | + | + | 1F. | – | — | 2·5 | 42·6 | +++ | | | Nil. | Good response to treatment. | Relieved. |
| 65 | 11 | F. | ++ | – | – | ++ | 2F. | – | — | 22·0 | 49·8 | +++ | | | Nil. | Good response to treatment. | Relieved. |
| 66 | 19 | F. | + | ++ | + | +++ | 2F. | – | Tired. | 22·5 | 39·6 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 67 | 18 | F. | +++ | + | +++ | + | 2F. | – | — | 4·5 | 16·2 | +++ | | | Nil. | Good response to treatment. | Relieved. |
| 68 | 21 | F. | +++ | + | – | + | 2F. | – | — | 10·5 | 24·6 | ++ | | | Nil. | Good response to treatment. | Relieved. |
| 69 | 25 | F. | + | – | + | + | 2F. | – | — | 19·0 | 37·0 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 70 | 25 | M. | +++ | + | +++ | + | 1F. | – | — | 1·0 | 6·0 | + | | | Nil. | Good response to treatment. | Relieved. |
| 71 | 30 | F. | ++ | ++++ | + | + | 1F. | – | Drowsy. | 9·5 | 41·1 | +++ | | | Nil. | Operation—laparotomy. | Relieved. |
| 72 | 8 | M. | + | + | ++ | + | 1F. | – | Confused, sleepy. | 14·0 | | ++++ | | | Nil. | Good response to treatment. | Relieved. |

[1] Fingers' breadth below the costal margin. [2] Milligrammes *per centum*. [3] King-Armstrong units. [4] Grammes *per centum*.

TABLE II.—*Continued.*

*Infective Hepatitis: June, 1949, to November, 1951.—Continued.*

| Case No. | Age. (Years.) | Sex. | Symptoms and Signs. | | | | | | Biochemical Findings (on Admission to Hospital). | | | | Liver Biopsy Findings. | Remarks. | Result. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nausea. | Abdominal Pain. | Anorexia. | Jaundice. | Liver Size.[1] | Bleeding. | Mental Condition. | Serum Bilirubin Content.[2] | Alkaline Phosphatase Content.[3] | Thymol Flocculation Test. | Prothrombin Index. | Total Serum Protein Content.[4] | | | |
| 73 | 35 | M. | + | ++<br>++ | + | + | 2F. | — | Delirious, Lethargic. | 17·5 | | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 74 | 25 | F. | — | — | — | + | 2F. | — | — | 9·5 | 15·0 | ++++ | | | Nil. | Good response to treatment. | Doubtful. |
| 75 | 38 | F. | + | + | + | — | 2F. | ++ | Anxious. | <0·2 | 6·3 | ++ | | | Nil. | Good response to treatment. | Relieved. |
| 76 | 22 | F. | ++<br>++ | — | — | + | 1F. | — | Lethargic. | 5·0 | 8·1 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 77 | 8 | M. | + | — | — | — | 2F. | ++ | — | 4·0 | 21·0 | ++++ | | | Nil. | Good response to treatment. | Relieved. |
| 78 | 48 | F. | ++ | ++ | ++ | ++ | 3F. | — | Nervous. | 47·0 | 46·5 | ++<br>++ | | | Nil. | | Unrelieved. |
| 79 | 44 | M. | — | ++ | ++ | ++ | 2F. | ++<br>++<br>+ | — | 40·0 | 28·8 | | 100 | | Nil. | Good response to treatment. | Relieved. |
| 80 | 16 | M. | + | — | + | + | 1F. | — | — | 10·25 | 18·3 | ++++ | 100 | | Nil. | Good response to treatment. | Relieved. |
| 81 | 10 | F. | — | + | — | ++<br>++ | 3F. | ++<br>++ | — | 9·5 | 8·4 | ++<br>+++ | 50 | | Nil. | Progressive hepatitis. | Died. |
| 82 | 24 | F. | ++<br>+ | ++ | + | + | 2F. | ++ | — | 4·0 | | | | | Nil. | Six months pregnant. | Relieved. |
| 83 | 14 | M. | — | — | ++ | ++ | 2F. | ++<br>+ | — | 9·5 | 10·2 | ++++ | | | Progressive hepatitis. | Progressive hepatitis, terminal necrosis. | Died. |

[1] 'Fingers' breadth below the costal margin. [2] Milligrammes *per centum*. [3] King-Armstrong units. [4] Grammes *per centum*.

some mechanical interference with the excretory function of the liver, such as excessive reabsorption of bile through the small bile duct channels or bile canaliculi. One sees a possible extreme example of this in the so-called cholangiolitic hepatitis of Watson and Hoffbauer (1946), a possible example of which was recently reported in the Australian literature. In the latter type there may be local lymphatic or circulatory derangements. The experimental work of the Mayo Clinic group (Gray, Mann, Gollman and Grindley) suggests that the ascites may be due to increased hepatic venous pressure resulting in distension of the thin-walled lymphatics and loss of lymph into the peritoneal space. They have shown that there is a close chemical similarity between hepatic lymph and ascitic fluid in liver disease. It would seem that circulatory factors may play an important part in the progress and outcome of liver disorders.

The importance of progressive hepatitis and its difficulty of recognition when physical signs are absent is not fully recognized. Kunkel, Labby and Hoagland (1947), members of the United States Naval Research Unit at the Rockefeller Hospital, New York, reported in 1947 a careful investigation and follow-up of 350 naval patients with infectious hepatitis; 290 or 83% recovered fully in under three months. Of the remaining 60, 47 had one or more relapses as evidenced by return of clinical symptoms and/or alterations in biochemical findings or the results of liver function tests. These relapses were associated with physical activity. All eventually recovered fully. The remaining 13 went on to chronic hepatitis. These workers concluded that the early detection of relapses and immediate restriction of activity might have been responsible for many of the full recoveries in the relapsing group.

We have had the opportunity of following the clinical and biochemical status of 11 patients in this series, a group of nurses in training at the Royal Prince Alfred Hospital. Most of these girls are well and at work, but suffer from such vague symptoms as languor, occasional nausea or abdominal discomfort. In hard-worked nurses in training these symptoms are difficult of assessment. The liver and spleen are not palpable in any of these girls. However, after seventy weeks the thymol flocculation test produces a persistently positive result in most cases, and the patient in Case 74 has a high positive result after 140 weeks.

Table III shows the biochemical findings in this group with an assessment of their clinical status.

This small group followed over a year amply illustrates our present lack of knowledge of the possible progress of the disease when the infection has clinically subsided. Knowledge can come only by a close and prolonged study of such cases over a number of years, so that the natural history of the disease may be determined.

The pathology of cases of progressive hepatitis is well known. The hepatic architecture is disorganized, and when the Masson staining technique is used, young fibroblastic tissue is seen in the portal spaces and spreading out into the hepatic lobules. Cellular infiltration mainly of the mononuclear variety is pronounced, around the portal tracts and in the sinusoids and around hepatic cells. New bile duct formation is commonly seen in the portal systems. As the disease progresses the cellular infiltration becomes less and the amount of fibrous tissue increases. Regenerating liver cells in groups may give rise to nodules, and the section has all the criteria of hepatic cirrhosis. Fatty infiltration is but rarely seen and is not a feature.

One frankly admits that in these progressive cases we do not know with any degree of certainty whether we are dealing with the same virus infection as that causing the infectious hepatitis that goes on to recovery. It is also possible that in these cases altered vascular or lymphatic or biliary excretory mechanics may determine the progressive nature. In transmission experiments in man in "chronic hepatitis" volunteers, no effective transmission by ingesting fæcal material has been achieved. At the moment then we do not know enough of the pathogenesis of progressive hepatitis to make any dogmatic statements, but it would seem rational in the present state of our knowledge to consider progressive hepatitis to be an occasional sequel of infectious hepatitis.

TABLE III.
*Serial Biochemical Findings in Series of Nurses.*

| Case Number. | Observation. | Weeks from Onset of Illness. | | | | | | | Clinical State. |
|---|---|---|---|---|---|---|---|---|---|
| | | 10 | 20 | 30 | 40 | 50 | 60 | 70 | |
| 6 | Thymol flocculation test result | − | ++++ | | | +++ | | | Well. |
| | Serum bilirubin content[1] | 0·2 | 0·2 | | | 0·4 | | | |
| 11 | Thymol flocculation test result | ++++ | | +++ | | | +++ | ++++ | Well. |
| | Serum bilirubin content | 0·2 | | | | | 0·2 | 0·5 | |
| 13 | Thymol flocculation test result | − | | | | − | − | − | Well. |
| | Serum bilirubin content | 0·8 | | | | 1·6 | 1·0 | 0·5 | |
| 15 | Thymol flocculation test result | ++++ | ++++ | ++++ | ++++ | ++++ | | | Well. |
| | Serum bilirubin content | | 0·4 | | | | | | |
| 33 | Thymol flocculation test result | ++++ | | − | | | | | Well. |
| | Serum bilirubin content | 0·4 | | | | | | | |
| 37 | Thymol flocculation test result | ++++ | +++ | +++ | | | | | Well. |
| | Serum bilirubin content | 0·8 | | 0·2 | | | | | |
| 43 | Thymol flocculation test result | ++++ | +++ | +++ | ++++ | | | | Not well. |
| | Serum bilirubin content | 2·5 | 0·8 | 3·0 | 0·8 | | | | |
| 67 | Thymol flocculation test result | − | − | | | | | | Well. |
| | Serum bilirubin content | 1·2 | 0·8 | | | | | | |
| 68 | Thymol flocculation test result | +++ | | | | | | | Well. |
| | Serum bilirubin content | 0·5 | | | | | | | |
| 74 | Thymol flocculation test result | − | + | − | + | | | ++++ | Not well. |
| | Serum bilirubin content | | 5·5 | 3·5 | 3·2 | | | 3·25 | |
| 76 | Thymol flocculation test result | ++++ | ++++ | | | | | | Not well. |
| | Serum bilirubin content | 0·4 | 0·4 | | | | | | |

[1] Milligrammes *per centum*.

In our series of 83 cases of infectious hepatitis, seven or 8·4% have shown definite evidence of progressive hepatitis.

Case 81 (a female patient, aged sixteen years) at autopsy was of particular interest, as all stages of hepatitis were seen ranging from recent central necrosis and collection of round cells and polymorphonuclear cells to nodular hyperplasia and dense fibrous tissue. The appearances suggested strongly that an active inflammatory process was going on all the time, and necrosis was seen even in liver cells which were apparently only recently formed.

The importance of recognizing relapses and treating them is fundamental.

A private case, not included in this series, is that of a young university graduate who had a mild attack of infectious hepatitis and returned to work and athletics after two weeks. During the following year he had no less than 15 episodes of mild icterus, nausea, the passage of light-coloured stools, disinclination for effort and lassitude lasting for three to six days, during which time he would rest and then feel well again. When treated with prolonged bed rest and after a long convalescence the results of his biochemical investigations returned to normal and the histological findings of his liver likewise.

*Effect of ACTH and Cortisone on Progressive Hepatitis.*

In an endeavour to find some agent that would halt the inexorable pathological changes in progressive hepatitis it was decided to try the effect of ACTH and cortisone. Active hepatitis is associated with considerable cellularity, both intralobular and periportal. Many of these cells are lymphocytes. It is known that ACTH and cortisone effect a reduction in circulating lymphocytes. Some authorities consider that the lymphocyte can proceed to a fibroblast, so that this was an additional theoretical consideration, in that ACTH and cortisone might prevent the development of young fibroblasts. Further, it has been demonstrated that in electrophoretic studies on patients with various diseases these hormones evoked profound changes in the plasma components, with a general tendency towards the return to a normal pattern with a rise in serum albumin level and a fall in serum globulin level.

The available literature on the subject is scanty, but the general agreement seems to be that the results are variable with improvement in some cases and no alteration in others.

Three patients in our own unit have been selected for cortisone or ACTH treatment and have been studied by the methods used by Hanger. The third case proved particularly interesting, as the progressive hepatitis was complicated by hæmolytic anæmia.

When the results of the use of ACTH in chronic progressive hepatitis in these three cases are summarized, it may be said that there was some temporary biochemical improvement, but this was not maintained when administration was discontinued. There was no clinical or histological improvement in the first two cases; the third patient improved clinically whilst under treatment with the drug, and hæmolysis was definitely reduced during this period.

One feels therefore that ACTH is unlikely to prove of much value in solving the problem of progressive hepatitis.

*Effect of Deep X-ray Therapy in Progressive Hepatitis.*

Following a discussion in the clinic, the question arose whether small doses of deep X-ray therapy to the liver area might prevent further fibrosis owing to the lymphocytic infiltration in progressive hepatitis. This has been attempted in two cases with negative results.

The use of ACTH and cortisone or deep X-ray therapy to the liver has not in our experience altered the course of the disease in progressive hepatitis, and we feel that the only therapeutic measure which is of undisputed value in this disease is bed rest. We have been impressed with the oft-repeated evidence of too early resumption of activities in those cases in which admission of the patient to hospital was necessary for recurrence of jaundice and progressive disease, and we feel that this fact is not fully realized by the medical profession generally.

In the American literature the value of bed rest in infectious hepatitis has been stressed by Snell, Neep, Hanger, Barker and others.

S. E. Bradley found that in normal subjects in the upright position and after exercise (treadmill) there was a considerable diminution in blood flow through the liver, as compared with the reclining posture. This may be an important factor in infectious hepatitis. It is also reasonable to assume that during exercise the metabolic functions

of the liver are considerably increased, and that oxygenation and nutrition of hepatic cells are further diminished.

The length of time during which one should keep the patient at rest would appear ideally to be until all clinical symptoms and signs had disappeared and the biochemical findings had returned to normal. However, we have been forced, in common with practice elsewhere, to allow patients up who had a persistently positive response to the thymol flocculation test, and we find that the result of this test may remain positive for many months. We are not altogether happy about this, as some of these patients have symptoms described by Sherlock and Walshe (1946) as the post-hepatitis syndrome.

### The Problem of Acute Hepatic Necrosis.

In a small proportion of cases of acute infectious hepatitis, death will occur from hepatic failure due to acute necrosis of liver cells. The process is often so rapid that regeneration of liver cells is practically non-existent. Death may occur early in the disease or during an exacerbation when smouldering hepatitis has been present for weeks or months, or as a terminal event in chronic hepatitis with hepatic cirrhosis. There appears to be no way of determining its occurrence, and very little has been presented in the literature concerning its prevention. It is recognized that it is more likely to occur in debilitated, undernourished persons, in pregnancy, and in those suffering from other chronic diseases. Fernando and Thanabalasunderam (1951) reported that of 135 cases of infectious hepatitis, 25 ended fatally with hepatic necrosis, and they showed that serious complications of a fulminant course and massive necrosis increased in frequency as the diets became more and more deficient in animal protein.

Massive hepatic necrosis has been reported in the experimental animal by many workers. Gyorgy defined two dietary factors, cystine and tocopherol, the absence of which in rats will generally promote the development of massive hepatic necrosis. Himsworth and Glynn's experiments produced similar results. In these experiments, great pains were taken to exclude infection as a cause of the necrosis. Himsworth believes that dietary deficiency leads to severe swelling of the hepatic parenchyma and so disturbs the circulatory supply to the hepatic cells so that necrosis, at first centrilobular, occurs.

Gyorgy has demonstrated that aureomycin delays the development of massive hepatic necrosis in rats on deficient diets, and thought that by inhibiting the intestinal flora it might prevent the formation of bacterial metabolites with which the liver cannot cope in the absence of tocopherol or the "sulpha"-containing amino acids. He has also tested in rats the effect of other antibiotics—penicillin, streptomycin, polymyxin, "Chloromycetin", terramycin and sulphaguanidine. He found that streptomycin and terramycin were preventive but not to such a degree as aureomycin.

It has been shown by several investigators that ligature of the hepatic artery in animals results in death with severe hepatic necrosis. In dogs death is invariable. Histological examination reveals total destruction of the hepatic parenchyma, which is crowded with spore-bearing bacteria. Markowitz, Rappaport and Scott, of Toronto (1949), accidentally found that when the animals are protected by large doses of penicillin, death does not occur. This finding has been verified in several laboratories and is now generally accepted. One might reasonably conclude from these animal experiments that the administration of adequate quantities of penicillin is beneficial when the liver has been deprived of arterial blood. Gray (Mayo Clinic) adds supportive evidence. Fitts, quoted by Markowitz, found that aureomycin gave a higher proportion of recoveries.

It would appear rational then to give all patients suffering from infectious hepatitis or hepatitis from other causes an antibiotic such as aureomycin as a protective mechanism against massive hepatic necrosis. This would seem to be of especial importance in pregnancy, or when malnutrition or alcoholism or debility is present.

The following case history illustrates acute necrosis occurring in infectious hepatitis.

CASE 5.—A male patient, aged forty years, a single man, had been well until two weeks prior to his admission to hospital, when he complained of some lethargy and slight malaise, which were followed two days later by mild jaundice. He was examined on September 18, 1951, by his doctor, who found slight hepatomegaly with tenderness. The spleen was not enlarged. He gave no history of contact with infectious hepatitis or of having had injections or contact with hepatic toxins of any kind. A provisional diagnosis was made of acute infectious hepatitis, and the patient was advised to go home to rest in bed. On September 25 his doctor was called by the patient's sister, who said that she was worried about him as he was vomiting. His condition deteriorated and he was admitted to hospital.

On his admission to hospital he was found to be jaundiced and unconscious, and was roused only by painful stimuli. His tongue was dry and coated, respiration was rapid, and pronounced *fetor hepaticus* was present. No spider nævi, liver palms or skin petechiæ could be found. The liver could not be felt, and on percussion the area of liver dulness appeared diminished. The spleen was not palpable and there was no ascites. His pulse rate was 96 per minute, the pulse being regular and bounding; the blood pressure was 220 millimetres of mercury, systolic, and 90 millimetres, diastolic. Despite his comatose and apathetic state, he obviously had a hyperactive circulation. There were no abnormal central nervous system findings. The urine contained bile pigments, but no albumin, leucine, or tyrosine crystals. The biochemical findings on his admission to hospital were as follows: the serum bilirubin content was 27 milligrammes *per centum*, the thymol turbidity was 13·4 units, the serum alkaline phosphatase content was 21·3 King units, and the $\gamma$ globulin was 20·4 units.

The patient died despite vigorous intravenous therapy. Aspiration liver biopsy performed ten minutes after death showed the appearances of acute hepatitis with massive destruction of the liver cells (Figures II and III).

At post-mortem examination the liver weighed 665 grammes; the capsule was wrinkled and the liver substance was soft and mottled, with areas of yellow alternating with those of deep red. The bile ducts were examined minutely and found to be patent, and the gall-bladder was normal.

The problems of hepatic necrosis and progressive hepatitis are linked, as it is not uncommon to find recent necrosis occurring in post-mortem specimens from subjects who have died from hepatic cirrhosis or chronic hepatitis. Indeed, all stages of infectious hepatitis may be found in the one liver when a careful search is made. Furthermore, the so-called smouldering cases of hepatitis with or without jaundice, or those in which recurrence or recrudescence of the inflammatory changes occurs, are due to milder necrosis, usually confined to the zone around the central hepatic vein and able to recover fully at this stage. Our most effective remedies, therefore, remain preventive and our weapons bed rest, gradual resumption of activities, avoidance of hepatic toxins, provision of "hepatic cell sparers" and antibiotics.

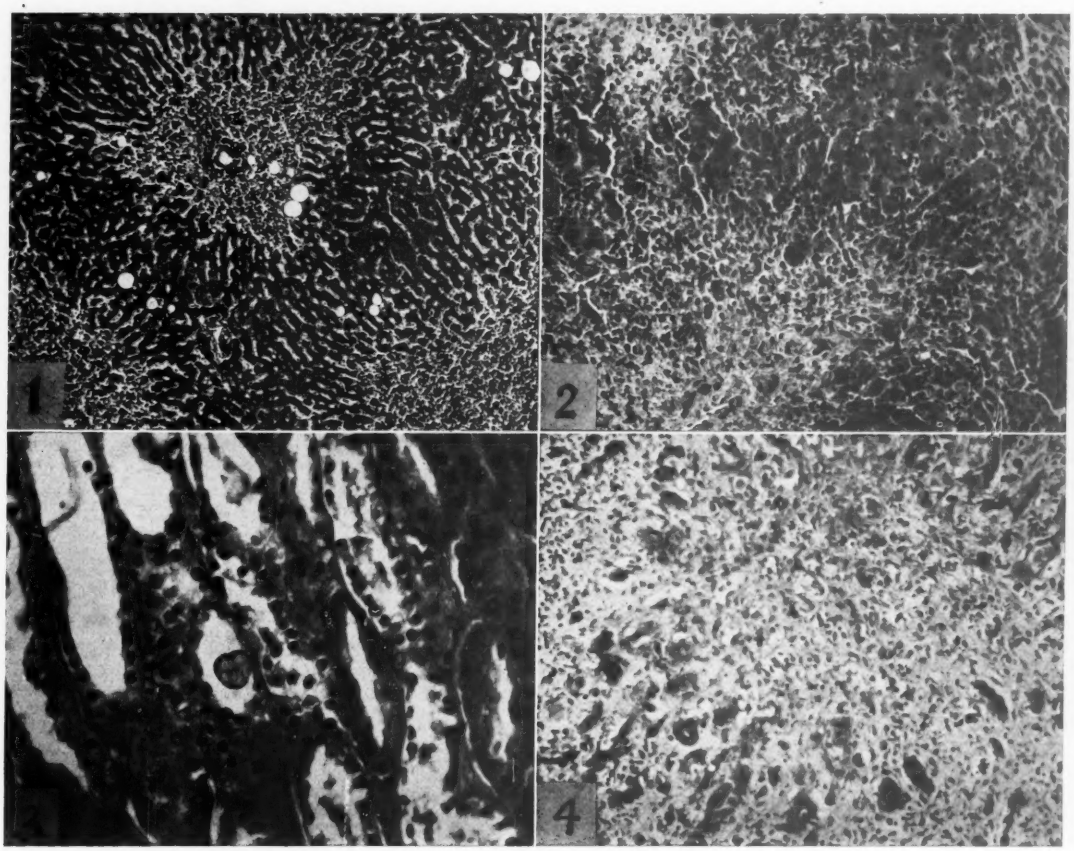
### CONCLUDING THOUGHTS.

An account has been given of some aspects of 83 cases of presumed infectious hepatitis at the Royal Prince Alfred Hospital over a period of twenty-nine months, and emphasis has been laid on the two major problems of acute hepatic necrosis and the steady progress of hepatitis to hepatic cirrhosis.

One wonders in what way further investigations will shed light on these unsolved problems. Will correlation of hepatic functions and structure based on liver biopsy studies provide the essential information, so that at present unrecognized histological features in association with more refined biochemical tests will provide adequate warning in those cases unlikely to follow the usual course? A more fruitful field may be the study of hepatic vascular physiology. Already splanchnic blood flow studies in man based on Bradley's technique are well advanced, and have been reported by Bradley and by Sherlock. However, results show considerable variations even at basal levels, and there is some doubt whether this method gives an accurate idea of the blood flow through the liver.

There are grounds for conjecture that the histological changes in progressive hepatitis are due, not to a continuation of the infective process, but to mechanical factors affecting intrahepatic blood and lymph flow (Pritchard, Bollman, Vonwiler).

## ILLUSTRATIONS TO THE ARTICLE BY STANLEY GOULSTON.




## ILLUSTRATIONS TO THE ARTICLE BY IAN HAMILTON.

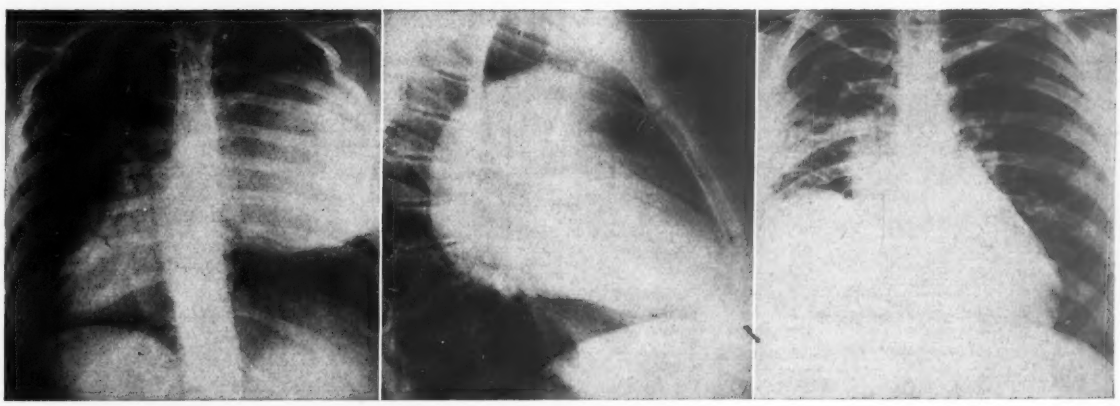


FIGURE I.

FIGURE II.

FIGURE III.

## ILLUSTRATIONS TO THE ARTICLE BY J. W. PERRY.

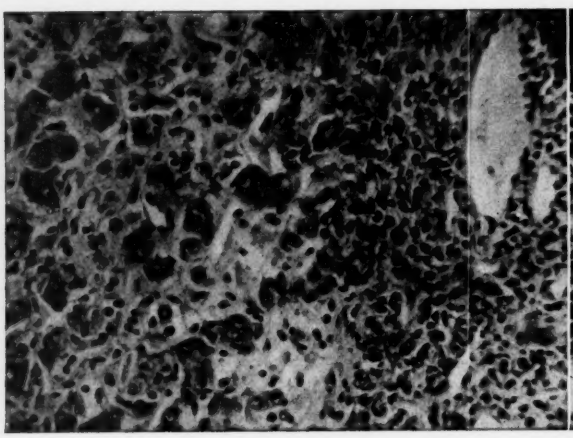


FIGURE I.

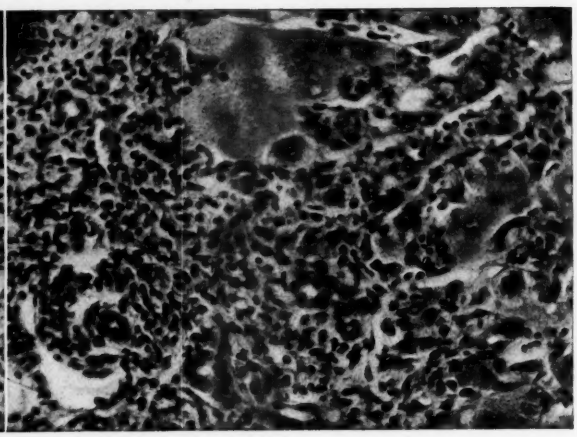


FIGURE II.

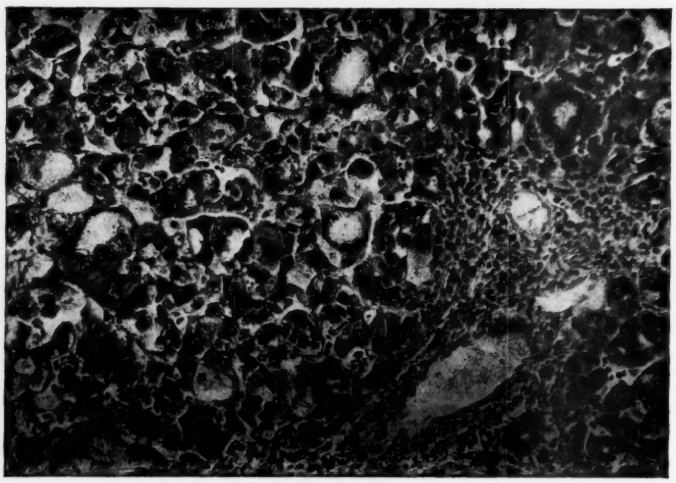


FIGURE III.

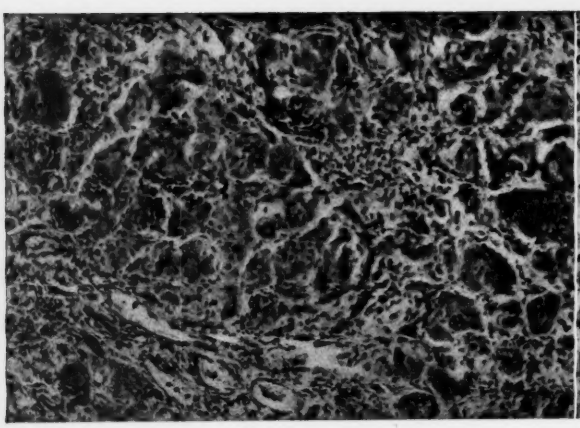


FIGURE V.

FIGURE VI.

## ILLUSTRATIONS TO THE ARTICLE BY FRANKLYN STONHAM.

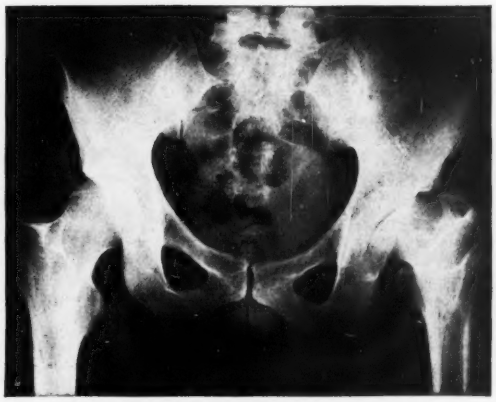


FIGURE I.

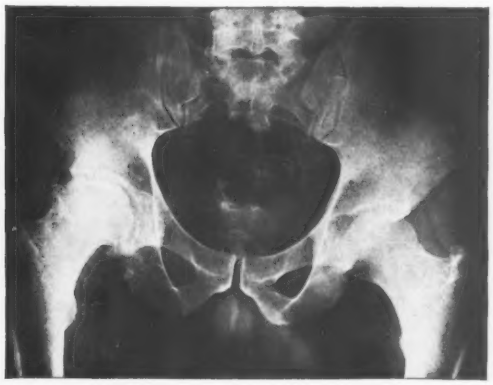


FIGURE II.

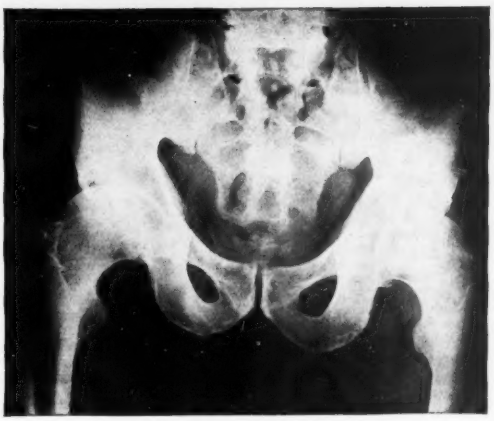


FIGURE III.

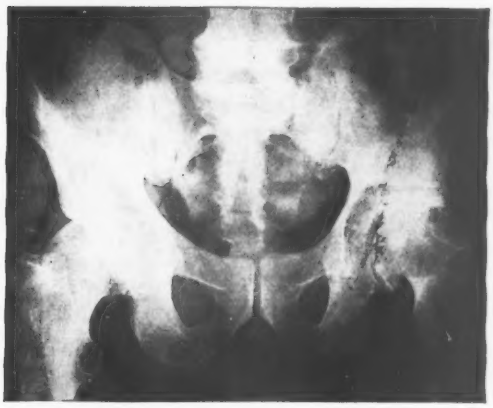


FIGURE IV.

## ILLUSTRATIONS TO THE ARTICLE BY A. BOLLIGER.

FIGURE II.

Coronal section of right adrenal of koala I. (×10.)

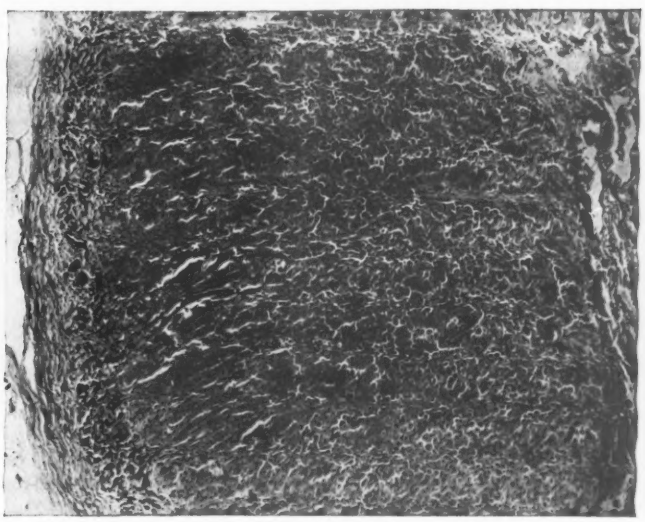
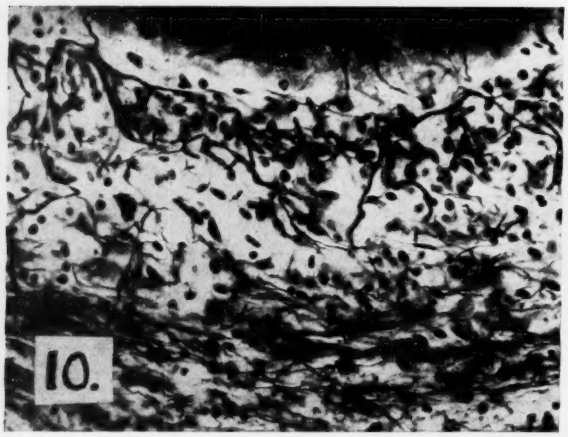
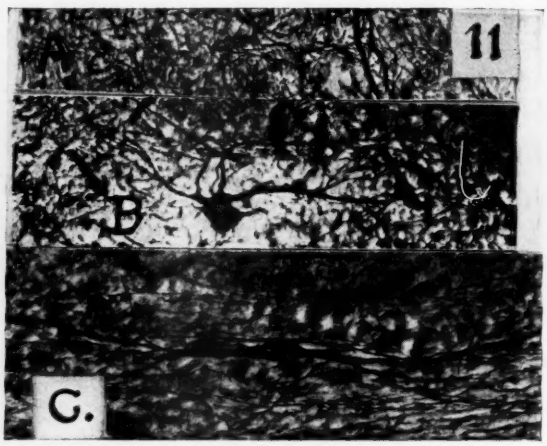


*FIGURE III.*

Cortex of adrenal from koala 1. (×75.)

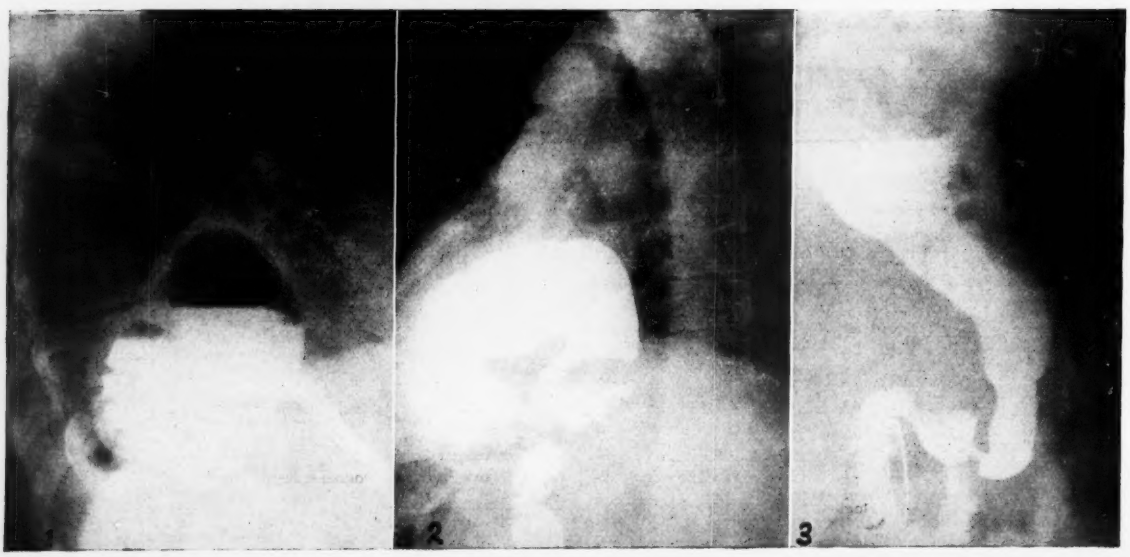
ILLUSTRATIONS TO THE ARTICLE BY ERIC SUSMAN, BRIAN TURNER, R. B. WILES AND OLIVER LATHAM.





ILLUSTRATIONS TO THE ARTICLE BY RICHARD FLYNN.



Will further information come from more specific liver function tests such as fractions detected by electrophoretic methods or perhaps by estimations of urinary excretion of porphyrins? Or will careful and painstaking metabolic studies by the use of such substances as radioactive methionine provide the answers?

We do not know what the future holds in store in the field of hepatic physiology and prevention of hepatic dysfunction and disease; but intense interest in these problems is world-wide, and one can confidently anticipate considerable advances in our knowledge in the near future. In the meantime we can continue to treat our patients on principles already determined by experience to be sound, with a view to protecting the hepatic cell from further damage and allowing it time for complete recovery. That great clinical maxim "rest to damaged or inflamed tissues" is never more true than when one is dealing with hepatitis, and it remains the foundation of our treatment of this disease.

ACKNOWLEDGEMENTS.

This paper is based upon investigations carried out by the Gastro-Enterological Clinic, Royal Prince Alfred Hospital, under the direction of Dr. A. W. Morrow, physician in charge of the unit, who himself cared for many of the patients and whose advice and help are gratefully acknowledged. I should also like to thank the following: Dr. C. R. B. Blackburn, Director of the Medical Research Unit, Royal Prince Alfred Hospital, for permission to record details of patients under his care and for helpful criticism; the honorary physicians at the Royal Prince Alfred Hospital, for permission to refer to patients under their care; Dr. Emily Day, who performed the biochemical tests on the group of nurses and kindly allowed me to record the results; Dr. Brian Billington, who performed the aspiration liver biopsies; and Mr. Woodward-Smith, of the Department of Medical Artistry, University of Sydney, for the photomicrographs.

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## Legends to Illustrations.

FIGURE I.—Acute infectious hepatitis. This section of liver shows central lobular necrosis with infiltration with histiocytes and leucocytes involving all lobules. (Hæmatoxylin and eosin stain, × 75.)

FIGURE II.—Case 5: Acute hepatic necrosis. This section shows zonal necrosis in all liver lobules around the central hepatic vein. There is very little liver tissue present and relatively little round-cell infiltration. There is no sign of regeneration and no connective tissue reaction. (Hæmatoxylin and eosin stain, × 75.)

FIGURE III.—Section of kidney at post-mortem examination. Acute hepatic necrosis. This section shows "leucine" crystals within the tubules occurring in a case of acute hepatic necrosis. (Hæmatoxylin and eosin stain, × 300.)

FIGURE IV.—Progressive hepatitis. Chronic advanced hepatitis uninfluenced by any form of therapy. At post-mortem examination sections of the liver showed areas of hepatitis in all stages from acute necrosis to advanced hepatic cirrhosis. (Hæmatoxylin and eosin stain, × 150.)

# HEPATITIS IN CHILDHOOD: A HISTOLOGICAL DIAGNOSIS.[1]

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DURING the course of routine biopsy and autopsy reporting the occasion often arises that the histological diagnosis, although reasonably acceptable, rests uncomfortably in the tableau of the complete clinical story.

It is my purpose to illustrate a number of examples of this—of a histological picture misleading or being misinterpreted, in some cases not providing the complete stimulus to further investigation.

Hepatitis is defined for the purpose of these remarks as a non-suppurative process characterized by zonal necrosis and a cellular response predominantly of the non-granular type.

There is no doubt that the initial acute stages are rarely seen in the autopsy room unless it is of the massive necrotic type, and further that in routine work, especially in the pædiatric field, the demand for biopsy study of the acute phase is not high. It is with the chronic form of non-suppurative hepatitis that difficulty sometimes arises.

General acceptance is given to the notion that chronic non-suppurative hepatitis is a better name than portal or Laennec's cirrhosis. Like chronic nephritis, this is the end result of a process of which the ætiological factors may be widely different. It is nevertheless a clearly defined entity, and is characterized by scarring and by hyperplasia of surviving liver cells and sometimes of bile ducts. The scarring may be gross and irregular or uniform and diffuse, depending upon the distribution and severity of the damage.

The practical result of this is that in a liver in which nodular hyperplasia and scarring are present, the condition is naturally assumed to be chronic non-suppurative hepatitis.

In some countries where malnutrition is prevalent the ætiological basis may be immediately obvious. In this country, if we remove the dietetic group of chronic liver disease, small when the pædiatric field is considered, there remains the natural temptation to attribute chronic hepatitis to the virus of infectious hepatitis. This is often abundantly justifiable, for when a case occurs in an epidemic and behaves clinically so as to suggest a subacute or chronic form of the disease, to such a diagnosis is as far as the histologist can proceed, and there is little doubt that he is correct. So far the virologist has been unable in spite of assiduous attempts to dispel that doubt by simple means.

The following cases illustrate a pathological and clinical picture fitting satisfactorily.

CASE I.—J.N., a female child, aged two and a half years, was admitted to the Children's Hospital, Melbourne, on August 11, 1948, with a history of jaundice of four days' duration. For one week prior to her admission her mother had noticed that the child's urine was dark and for five days that her stools were pale. Her appetite and general condition had been poor during this period.

Clinical examination of the patient revealed that her liver was palpable almost to the umbilicus and her spleen enlarged to six centimetres below the right costal margin. Apart from an eczematous rash over the legs, face and arms, the physical examination revealed no other abnormality.

Investigation of the patient revealed that a trace of bile pigment was present in the fæces. The serum alkaline phosphatase content was 21·5 units (normal, 3·0 to 20·0), and the bilirubin level was 7·5 milligrammes per 100 millilitres (normal, 0·2 to 0·8). The thymol turbidity was 10 units (normal, 0 to 4·0).

A blood examination revealed no abnormality. The bleeding and clotting times were within normal limits and the prothrombin index was 80%. A liver biopsy by the aspiration technique was then performed.

The picture (Figure I) was that of non-suppurative hepatitis. However, features suggesting post-obstructive jaundice were sufficient in the presence of equivocal results to liver function tests and persistently pale stools to warrant submitting the patient to laparotomy. This was performed nineteen days later, when a further specimen of liver was obtained.

It was noticed at this operation that the liver was enlarged, with an irregular surface, and was not deeply pigmented. A probe was introduced into the common bile duct and passed with some resistance into the duodenum. It was noticed that the common bile duct was thickened and had the appearance of a small artery. Examination of the second specimen of liver (Figure II) revealed an extension of the liver damage and some evidence of liver cell regeneration. One week after operation examination of the fæces by the Fouchet test produced a negative result, but eleven days later the result was strongly positive. Twenty days after operation the serum alkaline phosphatase content was 15·6 units, the serum bilirubin content was six milligrammes per 100 millilitres, and the thymol turbidity 16 units. Within a month of operation a repetition of the above-mentioned tests showed that the results had returned to normal limits.

This patient had a severe form of infectious hepatitis, the obstructive element predominating. Some features of this case are worthy of comment. In the first place, the gross liver enlargement accompanied by quite severe histological changes was followed by a return to a normal histological picture within eight weeks, although the liver remained palpable two centimetres below the right costal margin. It has been recorded previously (Lucké, 1944) that a complete return to normal structure occurs in acute hepatitis, but it appears that in young children damage may be more severe than in adults, although the capacity for complete recovery still remains. Secondly, the clinical and biochemical features of obstructive jaundice can be extraordinarily well mimicked by infectious hepatitis. Thirdly, as is becoming well known, the orthodox tests of liver function whose value is recognized in selecting obstructive from non-obstructive jaundice in adults are of less value in early childhood (Weller, 1951).

The second case is similar to the one reported above, but is recorded because laparotomy was also performed, and further, it is likely that if the histological diagnosis is correct, this child almost certainly contracted the virus infection *in utero*.

CASE II.—M.C., a female child, aged five weeks, was admitted to the Children's Hospital, Melbourne, on August 12, 1949, with a history of jaundice since birth and a failure to gain weight. Physical examination revealed her to be a small jaundiced baby whose liver was palpable three centimetres below the right costal margin. No further abnormality was noticed.

Investigation of the patient showed that bile was present in the fæces and that the serum alkaline phosphatase content was elevated to 28·5 units (normal, 3·0 to 20·0). The serum bilirubin content was 7·4 milligrammes per 100 millilitres (normal, 0·2 to 0·8) and the thymol turbidity was less than one unit (normal, 0 to 4·0). Examination of the peripheral blood revealed a normal picture. and the child's blood failed to react to the Wassermann test. The mother, father and child were Rh-positive. The plasma prothrombin index was 40% and the total serum protein content was 6·7 grammes per 100 millilitres; the albumin content was 4·1 grammes and the globulin content 2·6 grammes. One month after her admission to hospital the child's condition had not altered appreciably except that the spleen had become palpable. A transfusion of blood was administered in view of the prothrombin level of 40%, and laparotomy was performed.

At this operation the liver was found to be enlarged, but the surface was smooth. No extrahepatic biliary obstruction was encountered, although it was noted by the surgeon that the common bile duct was thick-walled. A ureteric catheter passed freely upwards toward the *porta hepatis* and into the duodenum below. A fragment of liver was obtained at biopsy, and examination of the specimen revealed non-suppurative hepatitis in the stage of repair (Figure III).

After operation gradual recovery took place and the child was discharged from hospital a month later, when liver function tests gave the following results: serum bilirubin content 0·6 milligramme per 100 millilitres; serum alkaline phosphatase content 6·5 units; and thymol turbidity less than one unit. The plasma protein content and the albumin-globulin ratio were normal.

[1] Read at a meeting of the Section of Pathology, Bacteriology, Biochemistry, Experimental Medicine and Forensic Medicine, Australasian Medical Congress (British Medical Association), Eighth Session, Melbourne, August, 1952.

These two cases illustrate an unusually severe type of infectious hepatitis in childhood, with a course longer than usual and with features closely simulating obstructive jaundice. The histological diagnosis is the complete diagnosis, and although it was not made with confidence in the first case, in the light of two subsequent liver biopsies it has been adequately confirmed in retrospect.

The work of Drake *et alii* (1952) in Philadelphia has given some hope to the ultimate attainment of an ætiological diagnosis, and Wolman (1950), of the Philadelphia Children's Hospital, has examined babies in whom there was proof of the transmission of virus hepatitis from the mother to the child *in utero*.

The following case is one in which this process probably occurred. It is the earliest such case to be recorded at the Children's Hospital, Melbourne, and to my knowledge the first to be recorded in Australia.

CASE III.—Baby S., the second child of a healthy family, born three weeks prematurely, was admitted to the Children's Hospital, Melbourne, on April 6, 1949, immediately after a precipitate delivery.

The child was cyanosed, and collapsed and died soon after admission to hospital. A post-mortem examination performed twenty-nine hours after delivery revealed a small liver with an irregular nodular surface (Figure IV). The liver substance was not bile-stained. Examination of the lungs revealed patchy consolidation consistent with hæmorrhage into the lung substance and inhalation of amniotic fluid. Examination of the liver showed the histological appearance of nodular hyperplasia (Figure V), indicating that the hepatitis had been progressing for some time *in utero* before precipitate delivery. However, diagnosis is rigidly histological, and in spite of the exclusion of syphilis and blood group incompatibility it is sadly devoid of proof.

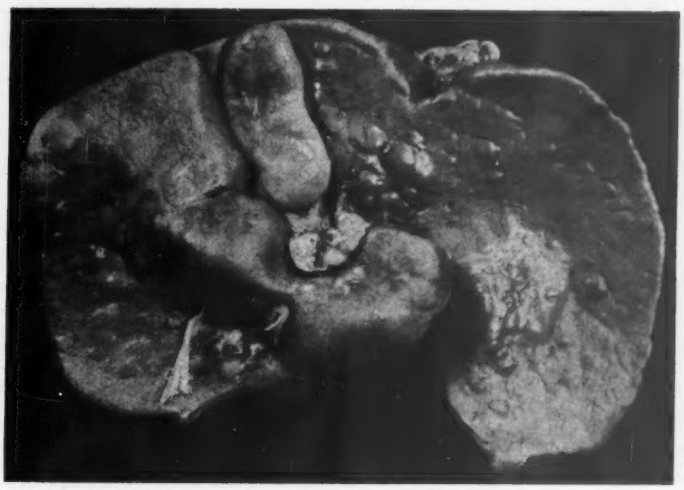

FIGURE IV.
Case III: Photograph of liver from Case III, showing the irregular surface due to nodular hyperplasia.

It may be said that the three cases so far recorded justify the diagnosis from the summation of criteria; but a further two cases, which will be reported more fully elsewhere, together with the results of some experimental work, demonstrate the flimsy structure of chronic hepatitis as a diagnosis, especially if it is too often reconciled with a virus ætiology.

CASE IV.—G.R., a male child, aged three months, was admitted to the Children's Hospital, Melbourne, on December 13, 1948, with a history of failure to thrive. His weight at birth was seven pounds twelve ounces, and on his admission to hospital was six pounds thirteen ounces. Since birth the child had been a slow and difficult feeder, and he had been artificially fed from the age of a few days.

Physical examination revealed him to be a pale baby whose liver was enlarged to six centimetres below the right costal margin and whose spleen was enlarged to three centimetres below the left costal margin.

Investigations gave the following information. The hæmoglobin value was 12·2 grammes per 100 millilitres, the leucocytes numbered 22,800 per cubic millimetre, and the differential leucocyte count revealed a polymorphonuclear leucocytosis. The serum bilirubin level was not increased, the thymol turbidity was eight units and the serum protein content was 4·8 grammes per 100 millilitres. The child remained in hospital for seven weeks, and although liver biopsy was anticipated, the development of *Salmonella derby* enteritis precluded this, and his condition slowly deteriorated and death occurred with unexpected suddenness.

A post-mortem examination revealed bronchopneumonia of moderate severity and changes in the terminal portion of the ileum consistent with mild enteritis. The liver was enlarged and firm and its smooth surface was replaced by a regular fine granularity.

The microscopic picture (Figure VI) was that of chronic hepatitis with evidence of nodular hyperplasia. The histological diagnosis was tested against the ætiological background of virus hepatitis. This possibility was acceptable, with the provision that the inflammatory process to have become so advanced may have commenced *in utero*.

The debatable part played by Rh factor iso-immunization in chronic hepatitis in childhood (Gerrard, 1952) must be assessed in this case. In the absence of any neonatal disease suggesting *icterus gravis* this was not seriously considered.

The result was that none but a histological diagnosis was made until some two years later, when the patient's sister was admitted to the Children's Hospital, Melbourne, with a disease closely resembling that of her brother. Liver biopsy revealed an identical pattern, and subsequent investigation showed that the second child had galactosuria, and a galactose tolerance curve confirmed this metabolic abnormality.

It is not the purpose of this communication to discuss fully the condition of galactose intolerance, as the second case will be reported fully elsewhere. Suffice it to say that other examples of this disease have almost certainly been overlooked, as was Case IV in this communication.

### Discussion.

The group of ætiological agents contributing to liver disease and jaundice in the neonatal period is extensive. Physiological jaundice has usually disappeared at the end of a week and Rh factor iso-immunization can be recognized by laboratory tests. The virus of infectious hepatitis is probably the next most common cause of neonatal jaundice in this community. It is hoped that future work in the field of virology will produce a simple method for making a rapid diagnosis in this disease.

The problem not infrequently arises in the Children's Hospital, Melbourne, of deciding whether neonatal jaundice is due to hepatitis or to developmental obstruction. It may be impossible to make a decision in some cases without laparotomy. There seems no doubt that operations have been performed upon children diagnosed as having a developmental obstruction who have been suffering from diffuse hepatitis. In some of these cases the impression of cure has been obtained by the passage of a probe into the bile duct. Our scanty knowledge of the involvement of the extrahepatic biliary system in virus hepatitis is testified to by the remarks of the surgeons concerning the bile ducts in Cases I and II. There may have been a swing too far from the views held by pathologists until about fifteen years ago that infectious hepatitis, then called catarrhal jaundice, was associated with swelling of the mucosa of the duodenum and biliary channels. The predominance of obstructive features in some cases of neonatal hepatitis may be explained by narrowing and inflammatory swelling of already small duct systems. That both pathologists and surgeons should acquaint themselves with extrahepatic changes in infectious hepatitis is most necessary.

Liver damage in acute infective enteritis, dietetic deficiencies, syphilis and galactose intolerance must be considered as an ætiological agent in neonatal jaundice. The histological picture becomes less characteristic with the developing chroncity of the disease produced by a variety of agents. It is therefore important to consider a range of causes while the patient is still alive to be investigated.

### Summary.

1. Attention has been drawn to the difficulty which occasionally arises in determining the ætiology from the histological picture in childhood liver disease.

2. Two cases of severe infectious hepatitis with fitting histological pictures have been described.

3. A case of probable intrauterine infection with infectious hepatitis is recorded.

4. Two cases of galactose intolerance have been mentioned in which the histological picture was that of chronic hepatitis.

### Acknowledgements.

I am indebted to the members of the honorary medical staff of the Children's Hospital, Melbourne, for permission to quote from their case records. Mr. Ernst Matthei, of the opto-mechanical section, faculty workshops, University of Melbourne, prepared the photomicrographs.

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### Legends to Illustrations.

FIGURE I.—Case I: Photomicrograph of liver biopsy obtained by aspiration fourteen days after the patient's admission to hospital. Destruction of liver cells and non-granular cell response are visible. On the right a portal tract shows greatly increased cellularity. (Hæmatoxylin and eosin stain, × 265.)

FIGURE II.—Case I: Photomicrograph of specimen of liver obtained at operation for inspection of liver and extrahepatic biliary system. Extensive loss of liver cells is evident, the inflammatory cell infiltration is more intense, and some surviving liver cells have multinucleate forms characteristic of hyperplasia. (Hæmatoxylin and eosin stain, × 265.)

FIGURE III.—Case II: Photomicrograph of a specimen of liver obtained at exploratory laparotomy. The striking feature is the variation in size of liver cells, with some multinucleate forms. In the portal tract connective tissue increased cell density is apparent, owing to infiltration with non-granular cells predominantly. (Best's carmine and hæmatoxylin stain, × 265.)

FIGURE V.—Case III: Photomicrograph of specimen of liver obtained at post-mortem examination. The disturbed architecture is the result of liver cell damage and death with nodular hyperplasia. Multinucleate forms are present and the portal tract connective tissue is increased in density. Islands of extramedullary hæmatopoiesis are visible, but are more discrete than the background of non-granular inflammatory cell infiltration. (Hæmatoxylin and eosin stain, × 265.)

FIGURE VI.—Case IV: Photomicrograph of liver obtained at post-mortem examination. There is gross distortion of normal liver architecture, with greatly increased cellularity and fibrosis of the portal tracts. There is apparent hyperplasia of bile duct elements. The nodules of liver cells show variation in size and shape and large vacuole fat accumulation. (Hæmatoxylin and eosin stain, × 265.)

## OSTEOARTHRITIS OF THE HIP JOINT.[1]

BY FRANKLYN STONHAM,
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OSTEOARTHRITIS is a degenerative process not associated with bacterial invasion or toxæmia, of which there are a number of clinical types.

1. Osteoarthritis may follow pædiatric disorders of the hip joint, such as congenitial dislocation, congenital *coxa vara*, *osteochondritis juvenilis* and slipped epiphysis. The symptoms are variable, but pain may be slight or even absent in the presence of gross anatomical distortion, and there may even be no history forthcoming of the patient's having been treated for a disorder of the hip in childhood. (Figure I.)

2. Osteoarthritic changes may follow traumatic dislocation of the hip or fractures of the acetabulum or of the upper end of the femur, especially if some degree of malunion occurs. (Figure II.)

3. Osteoarthritis of the hip as an isolated joint lesion is fairly common, and may occur in healthy young adults, but is more common in old age. Degenerative changes in other joints may be absent or inconspicuous. (Figure III.) Osteoarthritis of the hip joint may occur as a manifestation of generalized osteoarthritis.

4. Many joints may show evidence of degenerative arthritis, especially the hips, spine and knees. Often severe symptoms are present in one hip joint though X-ray examination shows both to be involved, and it is on account of the pain in the hip that the patient seeks relief. (Figure IV.)

### Morbid Anatomy.

The cause is unknown. Trauma, especially repeated minor trauma, has been blamed, since the condition is common in manual labourers; however, it occurs in a significant proportion of sedentary workers and also in persons suffering from such conditions as congenital cardiac disorders, tuberculosis *et cetera* who have led a life of restricted activity. However, local avascularity is a conspicuous feature and a definite and accepted underlying cause in those cases in which it follows previous hip disorders in the first and second groups; but there is no doubt that it is the common denominator in all types. An obscure ætiological factor interferes with the nutrition of the articular cartilage, and it is unable to withstand ordinary wear and tear. It becomes greyish, granular and shaggy, first over the weight-bearing surface of the upper portion of the femoral head, and finally it disappears completely and exposed bone remains. Similar changes follow in the remainder of the cartilage. Attrition occurs in the bone and it gradually wears away, a shiny surface being left with pits representing spaces formerly occupied by blood bessels. The underlying bone is fatty and atrophic. Similar changes occur in the acetabulum. The *ligamentum teres* may disappear, but occasionally it is hypertrophic and œdematous. At the periphery of the articular surfaces, where wear is minimal and there is a better blood supply, hypertrophy no doubt represents a perverted attempt at repair, and cartilage and bone growth produces "lipping", thickened cartilage, chondrophytes or osteophytes which may become detached to form intraarticular loose bodies.

The general tendency is towards flattening and mushrooming of the femoral head and towards *coxa vara* with corresponding distortion of the acetabulum. The joint capsule hypertrophies and is usually a quarter of an inch or more thick, and this thickening and the loss of elasticity limit movements and in some cases lock the joint completely. Bony ankylosis does not occur. Synovial fluid may be scanty or absent, but effusions of clear yellow or cloudy fluid containing débris and fat are not uncommon. The muscles operating the hip atrophy mainly from disuse.

### Clinical Features.

The main symptoms are pain, stiffness, and a stiff-hip, short-leg limp. The pain bears no relation to the degree of bony change and distortion revealed by X rays. Typically the pain is a dull ache accompanied by stiffness, and it tends to become easier with activity. It is often aggravated by exposure to cold and during cold weather. The pain may be subject to periodical variations, and during exacerbations it may be excruciating. The movements limited are rotation, abduction, adduction, flexion and extension in that order. Examination of the patient reveals fixed external rotation, adduction, flexion, lordosis and scoliosis. It is important to examine the condition of the muscles operating the hip. In cases in which there has been long-standing virtual ankylosis they may be very atrophic. X-ray examination shows the typical deformity—

[1] Read at a meeting of the Section of Orthopædics and Physical Medicine, Australasian Medical Congress (British Medical Association), Eighth Session, Melbourne, August 22 to 29, 1952.

a narrow joint space, sclerotic margins, lipping and possibly a certain amount of atrophy of the adjacent bone. It is important that all other suspected joints should be radiologically examined, since this is necessary in the planning of treatment.

### Treatment.

#### *Non-Operative Treatment.*

Rest in bed is indicated only during acute attacks of pain, otherwise it tends to favour increasing stiffness. Drugs other than analgesics are useless. Protein shock, vaccines, and gold and other injections have no influence on the course of the disease, and on the whole their use is disappointing. Manipulation, massage, infra-red irradiation and diathermy may give considerable but temporary relief from pain. Deep X-ray therapy is often a useful means of relieving pain, especially in cases in which bony changes are not pronounced, but its effect is unpredictable and the benefit is again temporary only.

Intraarticular injections of acid such as lactic acid or sodium acid phosphate together with procaine, or intra-articular injections of 1% "Novocain" solution alone give considerable immediate relief from pain, and a course of six or more injections at weekly intervals may give the patient acceptable relief lasting many months. This is at present probably the most popular form of conservative treatment.

Some patients whose symptoms are moderately severe may adjust their lives so that with the aid of analgesics and perhaps some other conservative treatment they can carry on a somewhat restricted activity without distressing discomfort.

Since no conservative treatment has any demonstrable effect on the course of the disease and the symptomatic relief is only temporary, it is contraindicated in the care of all patients who are otherwise fit to undergo operation and have an expectation of life of more than five years. It should not be even tried. Operative treatment has so much more to offer that it should be carried out early, and not after non-operative treatment has failed, the patient has become a chronic invalid and the disease has progressed.

#### *Operative Treatment.*

Cheilotomy, arthrotomy with joint *débridement* or removal of loose bodies, juxtaarticular drilling and the old *fascia lata* arthroplasty of J. B. Murphy have had occasional or limited successes, but these operations are all now obsolete. Joint denervation by section of the obturator nerve and the nerve to the *quadratus femoris* converts an arthritic joint into what amounts to a Charcot's joint.

*Osteotomy.*—Intertrochanteric abduction osteotomy permits correction of the flexion-adduction deformity and eliminates the apparent shortening. It reduces the strain brought about by walking and may bring healthy surfaces in the joint into weight-bearing apposition or relieve capsular tension; these results may explain the curious pronounced or complete symptomatic relief.

The operation is simple, and the modern operation in which a nail and plate are used to fix the bones abolishes the need for long recumbency and a plaster spica, which were formerly serious disadvantages. However, it does not restore movement, and the relief of pain lasts only about five years. It is indicated when there is useful movement with adduction deformity.

*Arthrodesis.*—Arthrodesis is certain in relieving pain, and the modern operation, in which fusion is effected by means of a long nail and bone chips or a bridge of solid bone across the joint line, obviates the need for fixation in a plaster spica. It does not correct fixed deformity, and it is unsuited to and is contraindicated in cases of bilateral disease. The loss of hip movement is compensated for by movement of the lumbar part of the spine, and if the spine is already arthritic the effect of the operation may be to transfer pain from one site to another or seriously to restrict the patient's activity.

*Arthroplasty.*—Arthroplasty gives the patient a painless movable joint. The operation is only slightly more severe than osteotomy or arthrodesis, and the period of convalescence is short. It is applicable to most cases, and its success depends largely upon the post-operative physiotherapy. After operation some patients experience pains about the groin and buttock. It should not therefore be undertaken if the muscles which move the hip joint are atrophic, or if a patient is too frail or is psychologically ill-adapted to cooperate in after-treatment. The operative technique is continually being improved, and with reasonable selection of cases failure to secure a useful movable painless joint should be uncommon.

### Summary.

1. Arthroplasty is the method of choice in the treatment of osteoarthritis of the hip joint.

2. Osteotomy and arthrodesis are occasionally indicated.

3. Non-operative treatment is palliative only and has no effect on the progress of the disease. It is indicated in the care of the "poor risk" patient with a short expectation of life, or when operation is refused. It is occasionally indicated as a temporary measure in very early cases in which there are slight disability and minimal deformity and restriction of movement.

## THE ADRENALS OF THE KOALA (PHASCOLARCTOS CINEREUS) AND THEIR ALLEGED RELATIONSHIP TO EUCALYPTUS LEAF DIET.

By A. BOLLIGER.

*(From the Gordon Craig Research Laboratory, Department of Surgery, University of Sydney.)*

IN 1919 MacKenzie and Owen, in a study on the glandular system of monotremes and marsupials, seemed to be impressed by the rudimentary nature of the adrenal tissue in the leaf-eating marsupials *Trichosurus vulpecula* (phalanger or common possum) and *Phascolarctos cinereus* (koala or native bear). They made the following statement: "The question is raised as to the association of a diminished adrenal activity with eucalyptus leaf diet and the possible advantageous use of extract of the leaf in disorders affecting the human adrenal gland."

Ever since MacKenzie and Owen made this highly speculative statement frequent reference has been made to the potential therapeutic value of eucalyptus leaves in adrenal insufficiency. For example, in 1924, Dr. Will Mayo, one of the founders of the Mayo Clinic, while in Australia, was told of the "rudimentary" adrenal glands of the koala and informed that the animal would die if it had not a continual diet of certain specific eucalyptus leaves and that in all probability these leaves were supplying the bear with a substance augmenting the insufficient internal secretion from the adrenals. After returning to the United States of America, Dr. Will Mayo retold this story, not only in private conversation, but also in public lectures.

Bourne (1934) reported upon the "unique structure in the adrenal of the female opossum (*Trichosurus vulpecula*)". He stated that "completely surrounding the medulla is a thin ring of cortex in which there is no *zona glomerulosa*". This statement of Bourne was quoted repeatedly in the scientific literature (Grollman, 1936 *et cetera*) and created or confirmed the impression that the adrenal glands of some of the leaf-eating marsupials are different from those of other mammals. According to this view, adrenal cortical insufficiency was alleged.

With the recognition of the great therapeutic value of substances such as cortisone derived from the adrenal, the adrenal glands of the leaf-eating marsupials, and particularly those of the koala, came into prominence again on account of the diet of the native bear, which frequently is confined to certain species of eucalyptus leaves. Thus in the *Saturday Review of Literature* of April 5, 1952, reference was made to this problem. Dr. Hench, the discoverer

of the therapeutic properties of cortisone, mentioned the possibility that perhaps some substance in eucalyptus leaves has adrenal cortical hormone activity (private communication from H. F. Hallman, M.D., Ph.D., of the Upjohn Company, Kalamazoo, Michigan, United States of America).

It is remarkable, however, that the adrenal glands of the koala have been examined by two authors only, and in both cases without reference to their weight. In a discussion of this matter with Sir Edward Hallstrom he suggested that the adrenals of the koala should be reinvestigated, and he supplied me with the corpses of three native bears.

### Previous Investigations.

MacKenzie and Owen (1919) made the following observations:

> The left adrenal is a flattened body ·75 to 1 cm in length and ·5 cm in greatest breadth . . . . The right adrenal is usually hidden by the liver which must be raised to bring it into view. It is a flattened body having similar measurement to the left adrenal, but it is not as a rule so well defined.

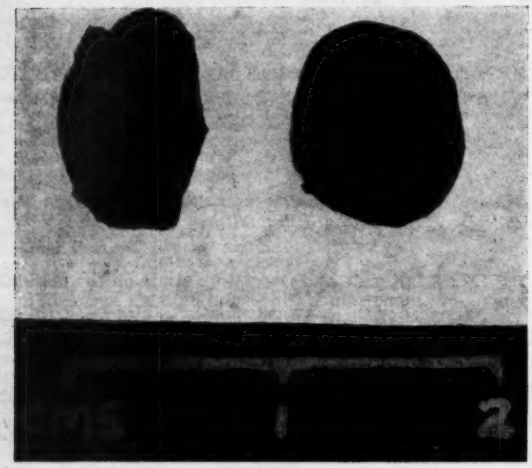

FIGURE I.
Right and left adrenals of koala I.

Bourne (1949), in his book "The Mammalian Adrenal Gland", makes the following statement:

> Two young males of *Phascolarctos cinereus* were examined . . . . Both the right and left adrenals are remarkable for their very thick capsules. In the left gland the capsule sent a number of very thick trabeculæ through the cortex towards the medulla. There was a fairly definite *zona glomerulosa*, which was well defined in places. The *zona fasciculata* was typical in some portions of the cortex and almost unrecognizable in others, in which regions also the *zona glomerulosa* ceased to be apparent. It was difficult to distinguish a *zona reticularis*, the inner portion of the cortex merging almost indistinguishably into the medulla. There was no obvious boundary between the two. The medulla showed no variation in staining capacity; there were a few sinuses but those present were small. The right gland was about the same size as the left gland. The cortex was thin, but appeared more definitely fasciculate and possessed a more definite *zona glomerulosa*. The medulla was much better defined than in the left gland, but the *zona reticularis* was not obvious. The medullary cells were aggregated in rounded bundles of varying size, and there were also a great number of sinuses.

Bourne gave no measurements or weights of the adrenal glands he examined. He also made no remarks as to the rudimentary nature or otherwise of the adrenals of the koala, but stated in the introductory paragraph to the chapter on adrenals in marsupials that they show surprisingly little difference from the eutherian mammals.

### Present Observations.

The first koala examined by us was a fully grown, well-nourished male of reproductive age, of body weight 8·25 kilograms, which had died from internal injuries from collision with a motor-car. The two adrenals weighed 510 milligrammes, the left one 280 and the right one 230 milligrammes. The adrenal tissue, therefore, amounts to 0·006% of the body weight. This is a comparatively small amount of adrenal tissue, because in most mammals the adrenals weigh from 0·01% to 0·02% of the body weight (Grollman, 1936). The weights of the koala's adrenals include also those of exceptionally thick capsules, and therefore the true adrenal tissue would be nearer to 0·005% of the body weight.

The left adrenal is a flattened, almost round, lentiform body measuring 1·0 by 0·9 by 0·55 centimetre in size. The right adrenal is a somewhat more elongated, ovoid-shaped body which contains on its surface four small outgrowths. It measures 0·9 by 0·7 by 0·45 centimetre (Figure I).

The cortices of both adrenals are of the usual mammalian pattern. They are about one millimetre maximum width. The *zona glomerulosa* is very distinct; the *zona fasciculata* is characterized by the presence of large amounts of yellow pigment. The *zona reticularis* is narrow and in many places practically absent. The outgrowths on the surface of the right adrenal consist of fibrous and adrenocortical tissue.

TABLE I.
*Showing Particulars of Koalas I, II and III.*

| Body Weight. (Kilograms.) | Weight of Kidneys. (Grammes.) | Weight of Adrenals. | | Ratio of Adrenal to Body Weight. |
|---|---|---|---|---|
| | | Left. (Grammes.) | Right. (Grammes.) | |
| 8·25 | 44·6 | 0·28 | 0·23 | 0·006 |
| 6·0 | 34·0 | 0·213 | 0·171 | 0·006 |
| 5·55 | 43·3 | 0·254 | 0·216 | 0·008 |

The medulla of both adrenals gave the impression that the usual ratio between large and small cells is in favour of the large ones, and that the capillary walls are thickened.

No accessory adrenal glands could be found.

The other two koalas (II and III) at our disposal were originally found in the bush in a weakened condition and then transferred to the Taronga Park Zoological Gardens, where they died soon after arrival.

The corpses of both these animals showed evidence of malnutrition. The weight of the adrenals and kidneys and the body weight of these two bears together with those of koala I are given in Table I. The adrenal tissue of koala II amounted to 0·006% and that of koala III to 0·008% of the body weight. Koala II therefore shows a similar adrenal body weight ratio to koala I. In koala III the adrenals, though still comparatively small, were relatively heavier than those of the other two bears; but this could be explained by the particularly poor condition of this animal—an assumption supported by the weight of the kidneys, which also seemed to be heavier relatively than those of the other two bears (Table I).

The histological appearance of the adrenals from koalas II and III was essentially the same as that of koala I (Figure II).

### The Adrenals of Trichosurus Vulpecula.

MacKenzie and Owen attributed rudimentary or hypofunctional adrenals to both the phalanger (*Trichosurus vulpecula*) and the native bear. It seems relevant to point out that the adrenals of the phalanger are relatively somewhat larger (range 0·008% to 0·015% of the body weight) than in the koala. The right adrenal of *T. vulpecula*, which, according to MacKenzie and Owen, may be absent, was always found to be present in a series of 60 phalangers examined by us. The *zona glomerulosa* was always present in adrenals of all male and female phalangers. This has

to be emphasized, because Bourne in his recent book (1949) has given no unambiguous direct correction of his earlier statement (1934), quoted above, to the effect that the *zona glomerulosa* is absent from female phalangers.

A number of phalangers or possums have been kept at our laboratory for several years without ever receiving any eucalyptus leaves in their diet. In spite of this, these animals remained perfectly healthy. Thus it has been proved experimentally that *Trichosurus vulpecula* does not require eucalyptus leaves in its diet, as suggested indirectly by MacKenzie and Owen, who held that this leaf-eating marsupial as well as the native bear (*Phascolarctos cinereus*) possesses constitutionally rudimentary adrenal glands.


### Summary.

The adrenal gland/body weight ratio of three male koalas (*Phascolarctos cinereus*) was below average values for mammals in general.

It is doubtful, however, if this can be interpreted as evidence of a constitutional adrenal insufficiency. Histologically the adrenals of the native bear are of the usual mammalian pattern, and functional investigations would be required to prove or disprove such an hypothesis.


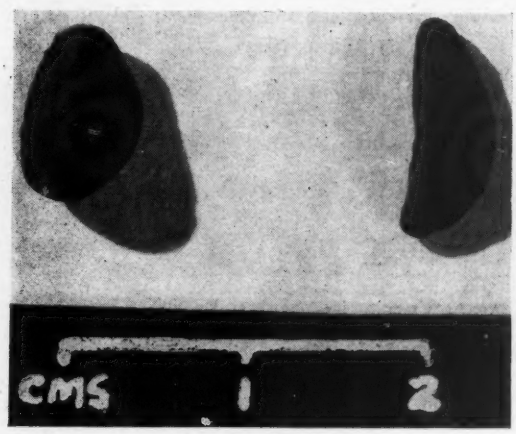


FIGURE IV.
Left and right adrenals of koala II.

There exists no evidence that eucalyptus leaves contain adrenal hormone-like substances. The preference of the koala for a diet of certain eucalyptus leaves may be determined by their availability, by their dietary suitability, or by other factors quite unrelated to adrenal function.

This question nevertheless merits further investigation. However, it has been proved experimentally that the phalanger *Trichosurus vulpecula*, the other leaf-eating marsupial referred to by MacKenzie and Owen as exhibiting "diminished adrenal activity", does not require eucalyptus leaves in its diet.


### Acknowledgement.

The author wishes to thank Sir Edward Hallstrom for the supply of the three koalas and for his interest in the investigation.


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# Reports of Cases.

## A CASE OF UNILATERAL CEREBELLAR DEGENERATION, WITH A NOTE ON THE GOLGI TYPE II NEURONS.


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AND

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PATHOLOGICAL FEATURES in cerebella both from clinical material and experimental studies are finding their way more and more into medical literature. Thus conditions which were once scarcely known are now becoming commonplace experiences to neuropathologists the world over. Until the last few years papers dealing with unilateral degenerations of the cerebellum were quite few, but this has changed, and well-known neuropathologists have been able to include such cases in their publications. Strong (1915) described a case very fully, and Kinnier Wilson, discussing cerebral lesions due to toxi-infective and vascular states in infants, described as occasional end results crossed cerebral and cerebellar atrophy. Others have noted gross cerebral lesions in much older folk as providing the same pictures, and the classical experimental work of von Monakow, who ablated one cerebral hemisphere in new-born puppies and got contralateral or crossed cerebellar atrophy, which effect was not produced on older puppies, is well known. Whatever the cause of the cerebral lesion—syphilis, arteriosclerosis, porencephalic or other cysts, virus infections or gross destruction—the cerebellar lesion is always degenerative. The cerebrum is the dominant factor; pathological cerebral states do not follow cerebellar abnormality.

### Preliminary Statement on the Present Case.

The post-mortem examination of the brain of F.B., aged sixty years, purported to reveal a normal cerebrum but an undersized left cerebellar hemisphere, which was hard on palpation. No other abnormality was observed in the cranial cavity. Other findings included pulmonary œdema, bilateral basal bronchiectasis and myocardial hypertrophy.

Unfortunately only the cerebellum, pons and medulla were reserved to us for examination. However, when microscopic examination revealed unilateral atrophy of the pontine nuclei and olive, widespread destruction of Purkinje neurons, basket cells and the granules, dentate nucleus, myelin centre, and the three peduncles, one had to consider the possible diagnoses of unilateral sclerosis of the cerebellum, unilateral olivo-ponto-cerebellar atrophy (although the granules and dentate nuclei were not affected in a case we published); or if microscopic examination of the cerebrum had revealed extensive neuronal degeneration, then crossed cerebral-cerebellar atrophy would have had to be considered.

### Clinical State of the Patient on His Admission to Hospital.

On August 24, 1951, at 5.30 p.m., F.B., aged sixty years, was admitted, cyanosed and moribund, to the Royal Prince Alfred Hospital. He died at 8.30 the same evening. The patient was unable to give a history of his illness, but his friends stated that for the past month he had become

increasingly breathless and bluish, and that one day before his admission to hospital he had complained of loss of power in the left arm and leg, dysphagia and dysarthria. An hour before his admission to hospital he had had a seizure, characterized by sudden tetanic spasm of all four limbs, which lasted thirty seconds. No history was obtainable at the time of past acute illness or disability.

On examination of the patient his temperature and respiratory rate were not recorded; his pulse rate was 84 to the minute, and the pulse was regular.

His radial vessels were tortuous and there was no obvious cardiac enlargement. Venous pressure was two inches above the *manubrium sterni*, and his blood pressure was 150 millimetres of mercury, systolic, and 90 millimetres, diastolic.

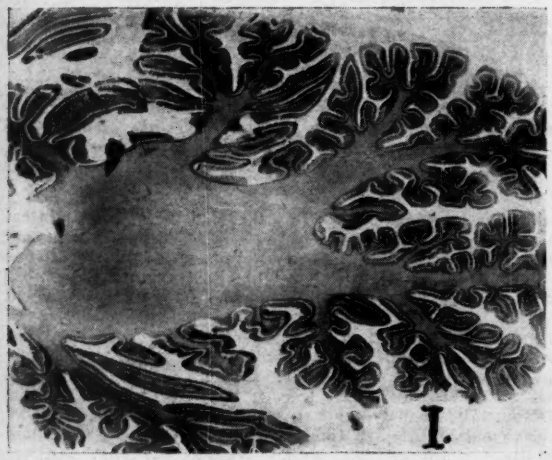


FIGURE I.
Parasagittal section of the right (normal) cerebellar hemisphere, about 1·5 centimetres from the mid-line, through its greatest length and just external to the denate nucleus. In the preparation the folias appear somewhat more discrete than normal. (× 2, Masson's stain.)

The trachea was in the mid-line and his respiratory movements were poor on both sides. There was no dulness on percussion, and air entry was poor, moist rales being present on the right side posteriorly.

The pupils were large and equal and reacted sluggishly. The patient was speechless and could not put out his tongue, which seemed to fill the whole mouth. The abdominal reflexes were present, but all tendon reflexes were absent and the plantar reflexes were flexor in type. Tonus was reduced in all four limbs, and sensation, so far as it could be tested, was normal. The general impression ruling was that the patient was *in extremis* with acute cardiac failure and cerebral ischæmia, leading to paralysis.

A lumbar puncture was performed and the spinal fluid was found to be normal in all particulars.

Some considerable time after the patient's demise Dr. Angus Holland succeeded in obtaining the following life history. He was born in New South Wales. He had been known to his housekeeper for thirty-five years; she was able to present the following particulars of his earlier life. He had never been able to walk normally during that period, and the defect had been growing worse. He always used to throw his left leg out antero-laterally as if he was doing a mild antero-lateral goose step with that leg.

During the war of 1914 to 1918 he was considered unfit for military service. During the last ten years he had been experiencing occasional cramps, with no special features except that they occurred in the left leg, thigh, hip and loin. During the period from 1915 to 1933 he drove sulkies for an ice company, working twelve-hour shifts, and thereafter for the same firm he acted as night superintendent, handing out milk to the carters, up to 1950. He never drove motor vehicles. Finally, for the remaining period before his death, he acted as cleaner and greaser to a wireless firm.

There was a history of alcoholism at times to the extent of his becoming violent. Intermittently during the last six years he had many attacks which clinically suggested hypertensive encephalopathy with pulmonary œdema. Early in his life he did some droving. The occurrence of venereal disease was denied.

This history perhaps rules out a severe condition of mental deficiency, and thus is of interest in evaluating evidence for and against a developmental anatomical defect in his central nervous system.

### Detailed Description of the Main Anatomical Lesions.

There is gross macroscopic reduction in the size of the left cerebellar hemisphere, with retention of the usual foliate structure of the cerebellar cortex. The right cerebellar hemisphere weighed 80·8 grammes and the left 30·5 grammes, while in parasagittal sections of the right and left cerebellar hemispheres in their largest and broadest measurements the right measured 5·0 by 3·9 centimetres, whereas on the left side the figures were 3·5 by 2·1 centimetres. Microscopic examination revealed that these changes were limited to the left side of the cerebellum, the *vermis cerebelli* showing very limited degenerative changes, and these being more extensive as the left side of the vermis was approached. The right hemisphere of the cerebellum was in all respects normal. Within the left cerebellar hemisphere it was noted that in the series of

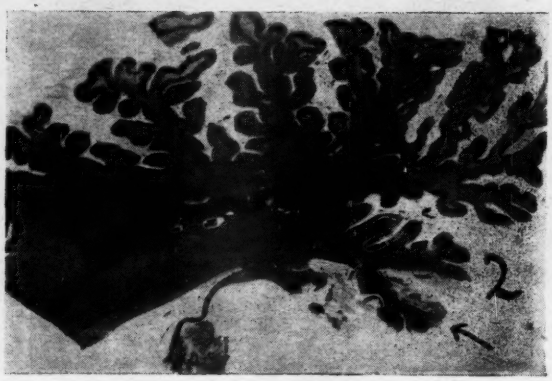


FIGURE II.
Similar section through the sclerosed left cerebellar hemisphere about one centimetre from the mid-line. It takes in the left dentate nucleus, in shape like a wavy line. The arrow points to a group of folias with residual Purkinje cells. (× 3, Masson's stain.)

parasagittal sections there was sparing from the degenerative changes in the flocculus. The transition from the cortex of the floccular lobe to that of the adjacent degenerative part was very abrupt.

The microscopic appearances of the left cerebellar hemisphere were as follows.

Whilst the cortex of the floccular lobe was in all respects normal the remainder showed pronounced changes. All the three layers were greatly reduced in size, with complete absence of the Purkinje cells. In the molecular layer there were a few residual ascending fibres together with some persistent cells which are either residual basket cells or Golgi type II neurons. The Purkinje layer was completely replaced by proliferation of the Bergmann glia. There were some residual horizontal fibres, some of which could be traced for a considerable distance. Some of these appear to be the axons of the few persistent Golgi type II neurons remaining in this layer.

The granular layer is very much reduced in size, with but few granules remaining; most of the nuclei are of glial nature. A few poorly developed mossy endings are present. Many Golgi type II neurons which were but slightly affected were present, and Freeman (1933) has

noted this latter phenomenon, which will be enlarged upon later.

The white core of the cerebellum is greatly reduced in size and shows some areas of cystic change. Silver preparations show fine fibres running in the direction of the cerebellar cortex, and many of these fibres show some degenerative changes. Actually many represent isomorphous with some anisomorphous glial fibres. The myelin loss in the folia themselves is more extreme than that obtaining in the larger cores of myelin tracts.

The left dentate nucleus has lost the typical main curved pattern and is reduced to a wavy line, while it is reduced in cellularity to approximately one-third of that on the right side. The residual cells are hyperchromatic and reduced in size, and many have eccentric nuclei. There is quite a pronounced glial reaction in the nucleus, leaving a fibrous glial feltwork in the place of the outfalls. It was noted that no neuronophagia could be seen taking place in this nucleus in any of the preparations. There are a couple of groups of neurons, some on the ependyma and some between them and the main dentate nucleus, which Mullendorff (1928) describes and which he considers part of the *nucleus globosus*, emboliformis being more external. These cells are of larger size than those in the dentate nucleus and appear intact, and but little gliosis obtains.

As far as could be determined from the piece of spinal cord presented, the spinal tracts were intact. Deformation of the brain prior to fixation had unfortunately deformed

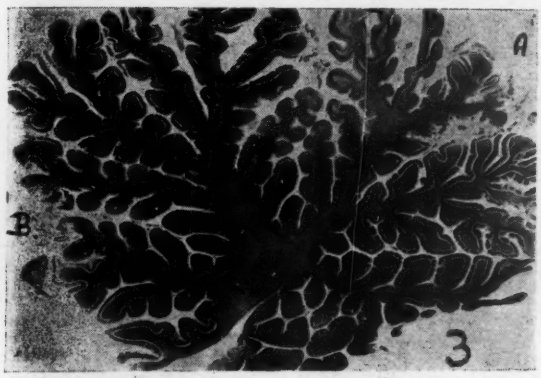


FIGURE III.

Sagittal section approximately through the centre of the vermis. Some groups of folias at "A" and one or two folias at "B" disclose sclerosis with absence of Purkinje cells. (× 4·5, Masson's stain.)

the brain stem to some extent, and the appearance suggested that the right pyramid was smaller than the left. However, further study showed this was in all probability an artefact.

Examination of a section just below the obex revealed that there was some slight diminution of the number of the ventral external arcuate fibres on the left side; the medial accessory olives and lateral reticular nuclei were intact. The arcuate nucleus on the left side could not be seen in sections at this level.

Examination of sections through the olivary nuclei reveals considerable reduction in the size of this nucleus on the right side, with some preservation of the normal foliate structure. The olivary neurons have almost completely disappeared. A few scattered cells remain in three areas: (*a*) in the ventral lamina medially towards the caudal end of the olive, that is, that portion of the main inferior olivary nucleus which projects to the tuber and pyramid of the cerebellum; (*b*) in the ventral part of the lateral lamina at approximately the mid-olivary level, that is, that portion which projects directly to the contralateral dentate nucleus; (*c*) in the medial end of the upper part of the dorsal lamina, that is, that portion of the main olivary nucleus which projects onto the superior *vermis cerebelli*.

Examination of the white core of the right olive reveals considerable reduction in the fibre numbers, and the perioliviary fibres are also much reduced. The foliate structure can be seen under higher power to be retained by virtue of the great increase of the glial elements. The olivocerebellar fibres can be seen to be very much reduced on the left side. The accessory olivary nuclei retained their normal cellularity. The lateral reticular nuclei were intact at this level. The tegmento-olivary tract and the central tegmental tract situated on the dorsal aspect of the olivary nucleus similarly seems smaller on the right side.

The sections at the level of the ninth cranial nerve not being directly transverse, it is difficult to form a true idea of the respective sizes of the inferior peduncles at this level. However, it is possible to confirm the decrease in the number of olivo-cerebellar fibres entering the left peduncle.

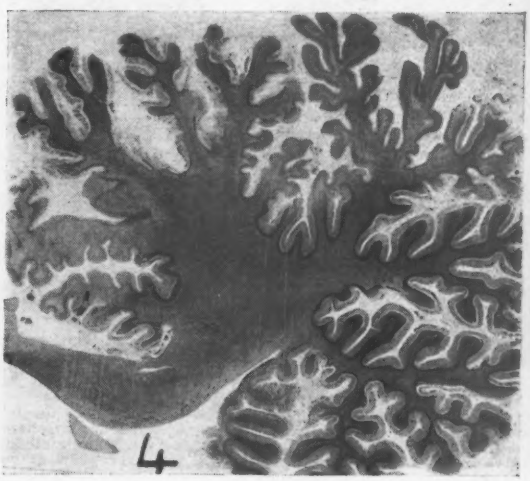


FIGURE IV.

Sagittal section through the junction of the vermis with left cerebellar hemisphere. Note the abrupt transition from the normal to the gravely sclerosed folia. (× 4, Masson's stain.)

The arcuate nuclei are both well seen at this level, and the ventral external arcuate fibres are well seen on both sides.

The vestibular nuclei also are intact.

Examination of a section through the pons showed that the neurons of this nucleus were severely reduced on the right side. Actual counts taken from paraffin sections stained by Masson's stain and from frozen sections prepared by Nissl's stain and also Cajal's silver gave such comparative numbers as 2500 on the right side and 8400 on the normal left side. A few large glial cells were noted with silver also among the degenerated neurons on the right. The nerve cells there were small, pigmented and atretic with displaced nuclei, and persisted throughout the area but in smaller groups.

The most obvious lesion in the tegmentum of the pons is the reduction in the size, especially supero-laterally, of the superior cerebellar peduncle on the left side. Also at this level in some of the Weil-stained sections can be made out a reduction of the size of the right tegmento-olivary fasciculus.

The sagittal sections through the cerebellar hemispheres readily reveal that the left middle cerebellar peduncle has a smaller area than the right.

### The Nature of the Atrophy.

In our approaches to this subject we have placed ourselves under a debt to Lichtenstein (1943, 1945), who has dealt carefully with atrophies, aplasias, hypoplasias and

dysplasias, and then has presented two of his own cases of crossed cerebro-cerebellar atrophy with a useful literature, and finally in another article suggests a carefully designed approach under 12 headings to the study of the diseased cerebellum. The large gliosis obtaining in all situations where gliosis is possible, and the definite remains of both original structure on macroscopic examination and neurons seems to preclude a developmental defect in our case. The absence of gross vascular effect would seem to exclude atherosclerosis and gross defect of blood supply. The absence of any observed evidence, save perhaps clinical evidence of cerebral lesions, leaves us with the task of comparing the evidence we have with such pictures of crossed cerebellar atrophy supplied by others or with the

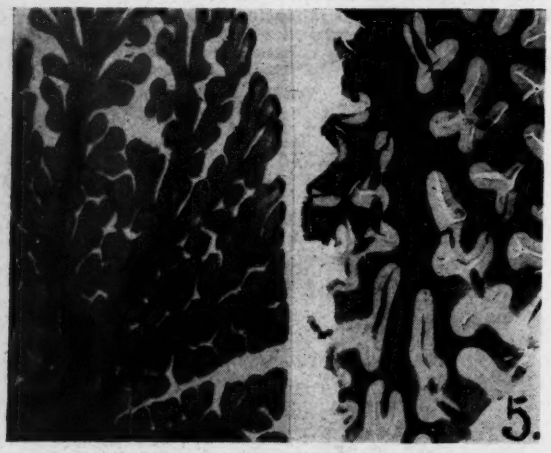


FIGURE V.

Paraffin sections from the left (sclerotic) cerebellar hemisphere, one left (× 4), and from the right (normal) hemisphere (one right) (× 5), both stained by Weil's myelin method. Grave demyelination is easily noted in the sclerosed section, but is not so pronounced in the main myelin centre.

lesions usually found in sclerotic and other affections of the whole cerebellum, with or without its spinal and brain stem connexions. All this is far from being a simple matter, for nearly every case except perhaps the rare group of lamellar degenerations seems to present lesions differing in varying degrees from those obtaining in the preceding ones examined.

### *Some Pathological Pictures of Crossed Cerebellar Atrophy.*

Lichtenstein's first subject was a female, aged thirty-four years, mentally affected for fifteen years and dead of pulmonary tuberculosis. Her post-mortem examination revealed hypoplasia of the right cerebellar hemisphere. In brief, a summary of her findings was hypoplasia of the right lobe of the cerebellum with normoplastic cerebellar folia. There was nerve-cell deficiency in the ventrolateral portion of the ipsilateral dentate nucleus and in portions of the contralateral inferior olivary body. A decrease in the size and number of nerve cells was noted in the pontine nuclei contralateral to the hypoplasia. Moderate gliosis was present in portions of the dentate nucleus, and the inferior olivary body was devoid of or deficient in nerve cells. More interesting still, since the cerebral tissues looked well on macroscopic examination, were focal areas of incomplete "ischæmic necrosis" in the cortex of both cerebral hemispheres. The red nuclei and thalamus not being cut in serial sections, no conclusion as to the exact status of the nerve cells receiving dentato-fugal fibres through the superior cerebellar peduncles could be reached. The illustrations from Weigert-Pal sections of the medulla, pons and affected dentate nucleus in this case closely paralleled our own.

Lichtenstein's second subject was an infant born with a spinal meningocele, which was afterwards repaired. Progressive enlargement of the head supervening, death occurred at the age of fifteen months.

At necropsy the findings were internal hydrocephalus, congenital absence of the *vermis cerebelli*, hypoplasia of the right cerebellar hemisphere, and dysplasia of some of the cerebellar folia. There were focal areas of microgyria in the frontal and in the occipital lobes.

The pathological findings were as set out earlier. In addition there was evidence that the accessory olivary bodies were bilaterally small, shrunken and almost entirely devoid of nerve cells. Portions of the right inferior olivary body (contralateral to the cerebellar hypoplasia) were similarly small, shrunken and devoid of nerve cells. A segment of the dentate nucleus (ipsilateral to the cerebellar hypoplasia) was deficient in nerve cells and rich in glial nuclei. As in the first case, the red nuclei and thalami seemed normal, allowing the omission of more complete examination.

In these types of cases Lichtenstein (1943) uses the term "maldevelopments of the cerebellum", although striking defects were found elsewhere in the central nervous system. He wishes to indicate that the cerebellar defects were primary and the changes in the olivary bodies, pontine nuclei *et cetera* secondary. However, lesions are variable from case to case. He further discusses the olivary bodies and the pontine and dentate nuclei in turn,

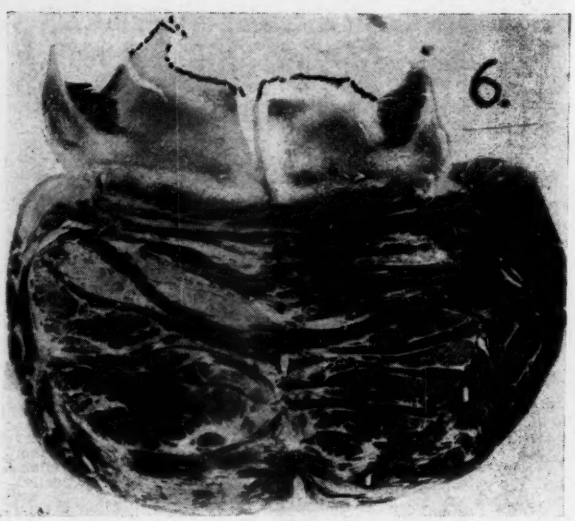


FIGURE VI.

Transverse section through the centre of the pons, slightly oblique, the left side being a little more cephalad than the right and possessing in the pontine nuclei over three times the nerve cells obtaining on the right side. The myelin cords to the right middle peduncle would appear to be more in evidence than those to the left middle peduncle, but efforts towards counting or measuring this difference were not successful. However, the areas available for holding pontine nerve cells were readily noted as much wider on the left.

and then under the term "pathologic differential diagnosis" investigates "crossed atrophy", parenchymatous cortical cerebellar atrophy, Friedreich's ataxia *et cetera*, and lastly, transneuronal degeneration, which seems to be held as proved. Josephy also reports on a case in which the right side of the body was small, with active knee jerks and pyramidal signs, and in which the post-mortem examination revealed atrophy of the right cerebellar hemisphere with scant Purkinje cells and granular layer, associated with considerable degeneration of the third layer of the left cereberal hemisphere, almost complete loss of Betz cells and also some affect of the *cornu ammonis* and thalamic nuclei.

Hassin (1935), in introducing his case, notes that atrophies are more common than inflammation, degeneration or tumours. They may be circumscribed or may be

concomitant with malformations or atrophies elsewhere in the central nervous system. He would have considered his case an example of sclerotic atrophy of the cerebellum were it not for the fact that there were changes in the contralateral cerebral hemisphere. The patient was a Negress, aged twenty-eight years, who died before any useful neurological examination could be made. However, her right arm was noted as being paralysed, deficient in tone and possessed of a tremor. A *résumé* of the lesions indicated that there was sclerotic atrophy of some lamellæ of the right cerebellar hemisphere with mild nerve and cell changes in the remaining parts of the cerebellum, save the semilunar lobe. Hassin made a point that many of the diseased Purkinje and Golgi type II nerve cell processes were tumified and that the white centres of the folia showed absence of mossy and climbing fibres and much gliosis. Scattered nerve cell degenerations were observed in pons and medulla, curiously enough, mostly on the right side. The left cerebral hemisphere showed sclerotic atrophy, the grey matter measuring 1·5 millimetres, compared with 2·0 millimetres in the right cerebral hemisphere. The right dentate nucleus showed loss of hilar and adjacent myelin fibres with gliosis. However, neurons were missing also bilaterally in frontal and occipital areas. Hassin's illustrations show the right olive and restiform body to appear smaller. He considers that the process started in the cerebrum and affected the contralateral cerebellar hemisphere secondarily. He concludes that crossed atrophy of the cerebellum is a combination of cerebral and crossed cerebellar lesions. The latter effect is strictly sclerotic. The cerebral lesion can be cysts, porencephalic lesions, or mere microscopic changes in the form of scattered nerve or cell degeneration of indefinite ætiology. On microscopic


FIGURE VII.

Slightly oblique transverse section of the dorsal half of the pons. The cores of myelinated fibres in the right superior cerebellar peduncle (R) are much denser and more numerous than those in the left (L), and the upper horn of its crescent is more complete in shape and size. The stain is Mallory's triple stain, and the myelin fibres come out light orange-yellow. (× 4.)

examination the cerebral changes are less intensive but more scattered and over wider areas, even in apparently healthy parts of the cerebrum.

Strong's patient had ataxia, uncertain gait, mental retardation and nystagmus. The following structures were affected: the left cerebellar hemisphere, the superior colliculus, the right inferior olive, the right central tegmental tract, the left *corpus restiforme*, the left middle cerebellar peduncle, the right pontine nuclei, the right pes, the right *substantia nigra*, the left dentate nucleus, the left superior peduncle and the right red nucleus. A number of intact structures were also enumerated.

From consideration of these cases it seems possible that our case most fits in with the diagnosis of crossed cerebral-cerebellar atrophy, some microscopic neuron outfalls in the contralateral cerebral hemisphere being postulated.

*The Golgi Type II Neurons.*

In this case the Golgi type II nerve cells have in the main survived and in a state of slight degeneration—a condition which Cajal called "preservation necrosis", and which he found after slight trauma. He mentions that the processes are slightly thickened and that a gum-like substance on the axon took on silver proteinate readily. This of course is true of other neurons, as in the conspicuous baskets in lamellar cerebellar sclerosis (Akelaitis, 1938). In ordinary sections of the cerebellar folia, the Golgi type II neurons can be made out in the layer of granules as small particles of protoplasm possessing a nucleus somewhat larger than those possessed by the granule nerve cells. They appear somewhat scanty in

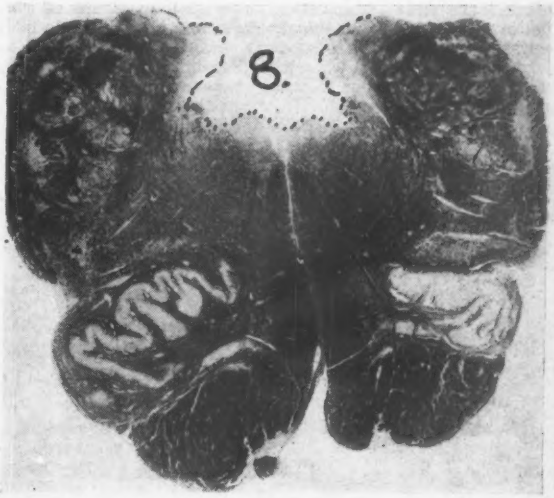


FIGURE VIII.

Transverse section of the medulla about the centre of the olivary nucleus. Marked atrophy of the right olive is seen, with some resultant distortion of the brain stem. Note the absence of the periolivary fibres. Dorsal to the degenerate olive a reduction in fibre density can be seen. This is thought to be due to degeneration of the tegmento-olivary tract. In the series of sections, the inferior peduncle can be seen to be reduced in size on the left side. (× 5; frozen section; Weigert-Pal myelin stain.)

number. Silver impregnations bring out the processes well; but in normal tissues myelinated fibres and the processes and bodies of other neurons quite obscure them. However, the almost complete absence of other neurons and myelinated fibres in the molecular, granular and innermost layers of the folias in this case and in others coming to our notice, particularly a case (1950) in which the heterotopias included numerous hypertrophied Golgi type II neurons, readily permitted a comprehensive view of these cells and their processes. As they increase in number and importance as one rises in the vertebrate scale, their survival value cannot be ascribed to their representing an archaic system. Freeman (1933) has reported similar findings, and in cases of swayback disease in lambs van Bogaert *et alii* (1950) noticed their survival when the granules and other neurons had degenerated. They are among the nerve cells which survive in the avitaminosis of chronic alcoholism, even when other neurons perish in the cerebellar lesions therein. However, in straightforward infarcts small and large in vascular diseases and in plaques in disseminated sclerosis, commonly all neurons perish. In Cajal's classification one recognized three classes of these neurons. Class A nestled near the Purkinje cells, sometimes had a small basket on their own, and had a dendrite quickly breaking up into six main branches in the molecular layer almost as conspicuous as the antlers of the Purkinje cells. The axon at once broke up into terminal branches in the layer of granules. The class B neurons

were spindle-shaped cells lying beneath the Purkinje cells and with long but few processes, some to the molecular and others to the granular layer. Class C, deep among the granules, sent a long axon to the molecular layer forming candelabra or horizontal fibres, while the other processes connected with the cerebellar glomeruli in the granules. About 1933, in one of his text-books, Cajal related that he had come to the conclusion that some of the stellate cells he had previously included among the Golgi type II neurons among the granules were in fact ganglion cells whose axon possibly left the cerebellum by one of the peduncles.

In his last book on pathological technique (1938), Mallory outlined the following method. A thin frozen section of nerve, biopsy material or cerebellum is taken from distilled water, preferably after formalin fixation, onto a large slide and blotted. Five or more drops of his 1% toluidin blue in 20% alcohol are then pipetted onto the section for from one to several minutes. Meanwhile a large coverslip is edged with "Vaseline" and laid with "Vaselined" side up on blotting paper, and several drops of distilled water are pipetted onto it. The stain is then smartly poured off the section and the latter on the slide

FIGURE IX.

Enlarged photograph of the left inferior olive from the previous illustration. The degeneration of the dorsal lip of the olive is complete, with retention of the original foliate structure in a contracted form. The lower lip containing some residual neurons has preserved its shape. Note the normal appearance of the median accessory olivary nucleus. The degeneration of the periolivary fibres can be seen. (× 20.)

is inverted and quickly applied to the watered coverglass and gently but firmly pressed down on the "Vaselined" coverglass, preferably with blotting paper. This Wright's chamber preparation in our case showed up the Golgi type II cells and their myelinated fibres quite clearly, since the replacement glia takes some time to absorb the stain and but few myelin fibres in all were present anywhere. In the white centre of the folia the separate myelin fibres, apparently slightly swollen, possibly represented a few mossy or climbing fibres, but many proceeded from or were proximal to the Golgi type II cell.

This procedure gives a useful picture when other neurons are few; it is not suggested that it can compare with the Golgi method. It gives a valuable picture of the spinal cord and brain stem. We may here mention that attention has been given to certain qualities possessed by certain groups of neurons over others. Wertham (1934) alludes to the lipophilic large Golgi type II neurons, and asserts they may be affected in phosphorus poisoning before the lipophobic Purkinje cells; he separates the behaviour of the nerve cells in the principal olives from that of those obtaining in the accessory olives. Other groups, such as those in various parts of the hippocampus, also have their individual behaviour.


## Summary.

1. A case has been presented wherein the patient presented over a period of thirty-five years clinical signs in his left lower limb, suggesting a possible cerebral and/or cerebellar lesion.

2. The post-mortem examination revealed sclerotic atrophy of the left cerebellar hemisphere and the left dentate nucleus, with slight involvement of the vermis and escape of the flocculus.

3. Other lesions included degeneration of the left inferior olive and right pontine nuclei, and reduction in the fibre content of the left superior, inferior and middle cerebellar peduncles.

4. The microscope confirmed these findings and showed practically complete absence of the Purkinje cells, granules and basket cells and fibres with sclerosis of the white centres of the folias and with escape of the Golgi type II nerve cells.

5. The cases of crossed cerebral-cerebellar atrophy described by other authors and their discussions thereon suggest this syndrome as a possible cause for the unilateral cerebellar lesion in our case, since the naked-eye absence of cerebral defects does not preclude microscopic lesions in the cerebellum. Nevertheless, in the absence of proved cerebral lesions, a diagnosis of unilateral cerebellar sclerosis only can be presented.



## Acknowledgements.

Acknowledgements must be made to Dr. E. S. Morris, Inspector-General of Mental Hospitals, New South Wales, and Dr. Grey Ewan, Director of Mental Hygiene, for permission to publish this case; to Professor W. K. Inglis and Professor A. N. Burkitt for their continued help and interest; to Miss Hazel Hunter, librarian, for looking up many references; to Mr. Woodward-Smith and Mr. K. Clifford, of the Department of Medical Artistry, University of Sydney, for the illustrations; and to Mr. T. Jones for some of the sections.


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### Legends to Illustrations.

FIGURE X.—A Cajal silver preparation from part of the sclerotic left cerebellar cortex showing the proliferated Bergmann glial nuclei and fibres, the absence of Purkinje neurons, and the paucity and thickening of the horizontal fibres and baskets, denoting partial degeneration. Note also complete absence of granule cells in the granular layer, and in lieu of regular axis cylinders the white centre holds fine fibres mostly glial, both isomorphous and anisomorphous, and a few myelin fibres. The blackened area at the top of the section above the arrow represents silver deposits on the Bergmann glia. (× 400.)

FIGURE XI.—Three silver impregnated sections from the sclerotic cerebellar cortex. "A" shows swollen tumified processes from such swollen presumably Purkinje cells, one of which is shown in "B", whilst the lowest section ("C") shows a fusiform Golgi type II neuron with but few processes, which at first lie below and parallel to the line of the Purkinje cells before attaining the molecular layer and the cerebellar glomeruli in among the granules.

FIGURE XII.—Cajal silver sections of groups of Golgi type II cells; about a dozen (× 200) in 12 "A", on the right, and about eight or nine in "B" on the left (× 400). They appear more plentiful since the area is contracted and the absence of granules permits a clearer view. Note on either side of the central line the rows of nuclei of the proliferated Bergmann glia.

## UPSIDE-DOWN STOMACH IN A PARAHIATAL HERNIA.

By RICHARD FLYNN,
*Sydney.*

MRS. C.B., aged fifty-five years, was admitted to Lewisham Hospital under my care on December 17, 1940, with a diagnosis of acute cholecystitis. Two nights previously she had been awakened from her sleep with severe pain in her epigastrium and right hypochondrium. The pain had doubled her up and had needed a hypodermic injection of morphine sulphate for relief.

She had previously been troubled with flatulent indigestion and heartburn after meals and had experienced similar attacks of colicky pain to the one for which she now sought relief. After she had settled down, a Graham's test was asked for. This was performed on January 9, 1941, and the late Dr. A. Oxenham reported as follows:

> Graham's test shows the gall-bladder to be a non-functioning and a pathological one and to contain several large calculi in its fundus and there is, also, some calcareous changes in the fundus itself.

An electrocardiogram taken at that time showed no significant changes.

On January 13, 1941, she underwent the operation of cholecystectomy, and a diseased gall-bladder with stones was removed. She enjoyed a normal convalescence.

She reported back on April 9, 1946, complaining of pain in the upper part of the abdomen, and her history suggested duodenal ulcer. X-ray examination with a barium meal was carried out by Dr. V. H. Hegarty, who reported as follows:

> The stomach is hour glass in type, there being a central constriction. No ulcer or filling defect due to neoplasm can be visualized and hour glass form is apparently due to adhesions or fibrosis from an old ulcer. The duodenal bulb is largely destroyed due to adhesions. There is also a diaphragmatic hernia of the stomach, through the œsophageal orifice of the diaphragm.

Her clinical condition at that time was as follows. She had considerable pain in the epigastrium; she was doubled up with pain, and her abdomen swelled up. After eating, if she did not vomit she got pain, which grew worse and was cramp-like. Her appetite was good and she enjoyed her food; she had no pain or difficulty in swallowing, but she could not take large meals. She could feel the pain coming on while she was eating. She had no history of jaundice. Her bowels were constipated, but moved daily with opening medicine.

To exclude any possibility of obstruction she was radiologically examined again, this time by the late Dr. C. Sim, who reported the following findings. The œsophagus occupied the usual position, except that it was pushed backwards somewhat by the hernial mass in its lower quarter. There was no obstruction at the cardio-œsophageal junction, and the fluid ran right through into the upper end of the stomach, which lay beneath the diaphragm in its proper place. The body of the stomach then turned completely upwards and backwards, to pass through a large defect in the middle part of the left cupola. The defect in the left half of the diaphragm was slightly posterior to the middle line. The pyloric portion reentered the stomach through the opening and lay in the abdomen.

In 1947 the patient went to live in the country, but on September 9, 1948, she returned on account of a malignant lump in her right breast. While she was in hospital awaiting operation, an X-ray examination of the chest was made to exclude metastases. The film was reported on as follows:

> There is some congestion of the lung tissue in the left costophrenic sinus. The films give a beautiful demonstration of a large diaphragmatic hernia, a large portion of the upper end of the stomach is herniated and presents an appearance of a large circular shadow, mostly behind the left ventricle and projecting somewhat beyond its lateral border. The sac shows air content in its upper half, then a fluid level and a fluid shadow in the lower half.

At that time the following report was made on an X-ray examination with a barium meal:

> There is a large portion of the cardiac end of the stomach herniated through the diaphragm which contains a considerable six-hour residue. The œsophagus appears to be somewhat elongated coming below the diaphragm, then a good third of the stomach is herniated and the pyloric end of the stomach is twisted upon itself and there is a very considerable delay in the evacuation of the meal through it. I can see no definite evidence of malignancy or ulceration.

A barium enema flowed freely through the large bowel back to the caecum without suggestion of herniation or other abnormality. The stomach was washed out to clear it of any residue, and a Ryle's tube was left in during the operation.

The patient's blood pressure was 150 millimetres of mercury, systolic, and 70 millimetres, diastolic, and an electrocardiogram showed no significant changes.

On September 27, 1948, I performed a radical removal of her right breast. She was given a blood transfusion, and her convalescence was uneventful. A pathological report on the specimen by Dr. Eva Shipton reads as follows:

> Microscopically: Sections of the growth show carcinoma. The histological appearance suggests that the growth started in a duct. The glands are not invaded by the growth.

I thought that, after she had undergone a radical mastectomy for carcinoma, and as the diaphragmatic hernia was not troubling her unduly, she should keep it, particularly as she was sixty-three years old. However, I advised her to carry a stomach tube so that she could relieve herself if the necessity arose.

She returned in October, 1952, requesting operation. Her history was as follows. She complained of vomiting and of pain in the upper part of the abdomen, which had been growing worse during the last twelve months, necessitating her admission to a country base hospital on three occasions. She said that she had had tetany associated with the vomiting on one occasion. She also said that she usually vomited about once or twice a wek, the vomiting being associated with pain in the left hypochondrium which radiated around to the back. She had noticed breathlessness when she was lying flat on her back, and also that she preferred to be on her left side as it was painful to lie on her right side. She had noticed dyspnœa when walking up hills, but had experienced no pain in her chest.

On examination of the patient, her blood pressure was 165 millimetres of mercury, systolic, and 80 millimetres, diastolic. Her heart sounds were normal and heard in all areas. Diminished breath sounds at the base of the left lung and bowel sounds were heard in this area. A test meal examination revealed pronounced hyperchlorhydria. The result of a urea concentration test showed 2·4% at the end of the second hour and 3·3% at the end of the third hour. The blood urea content was estimated at 45 milligrammes per 100 millilitres of blood. On microscopic examination of the urine, two granular and two waxy casts were seen. The hæmoglobin value was 14·0 grammes *per centum*. Radiological examination with a barium meal was carried out, and Dr. D. B. Wightman reported as follows (Figures I and II):

> The œsophagus is of normal length and the cardio-œsophageal junction is in the abdomen. The body of the stomach rotates upwards and comes to lie in the thoracic cavity. The pylorus is at the level of the diaphragm, and the duodenum runs vertically downwards. There is movement on the left side on respiration which is not paradoxical though not as as marked as on the right side.

On account of her increasing trouble it was decided to try to relieve her, so on October 27, 1952, through a thoracic approach I performed a radical cure of a diaphragmatic hernia. The hernia had a definite sac so well developed that it would make a large scrotal hernia blush. When the sac was incised it was found to contain stomach and spleen. The spleen was oozing from many fissures on its surface, so it was removed. It seemed that her increasing trouble was due to the spleen's excursions into the chest. Its removal controlled the bleeding and also gave the stomach the "right of occupation of the upper abdomen". The hernial sac was sewn up and treated as one would an inguinal sac. The hole in the diaphragm was parahiatal and was sewn up with silk. The chest was drained with a de Pezzer catheter inserted through a stab wound, and the thoracic wound was closed as is customary.

An X-ray examination of her chest on October 31 revealed a large opaque area obscuring the lower half of the left hemithorax. This extended to the level of the sixth left rib posteriorly and was thought to be due to fluid effusion and pleural thickening. This is a frequent finding both after repair of a diaphragmatic hernia and also after splenectomy.

On November 17 X-ray examination after a barium meal revealed that the stomach now lay below the diaphragm entirely. The mid-portion of the stomach exhibited constant narrowing when the patient was in the erect position, but this was not so when the patient was prone (Figure III). The appearances suggested that there was some fixation of the stomach in that region by peritoneal bands or adhesions. No definite intrinsic abnormality in that region could be detected, nor in the stomach or duodenum. Gastric evacuation was noted to be proceeding satisfactorily.

### Conclusion.

This case is reported because of the rarity of an upside-down stomach in a diaphragmatic hernia, and because it shows the gradual increase in size of the contents of the sac and in the degree of obstruction which they caused.

## GIANT DERMOID CYST OF THE MEDIASTINUM.

By IAN HAMILTON,
*Honorary Surgeon, Royal Adelaide Hospital, Adelaide.*

ON January 27 G.H., aged thirty-three years, was admitted to the Royal Adelaide Hospital under the care of Dr. Guy Lendon, with a history that eight weeks previously, on the day after she had done a heavy wash, she got a pain across the front of her chest. It lasted for two weeks. Seven weeks prior to her admission to hospital she had become short of breath and had vomited for two or three days. The pain in the chest came and went, and she was admitted to hospital and treated for bronchopneumonia. She had a wheezing cough in the morning, but little sputum. She had lost weight. Her appetite was good, her bowels acted satisfactorily, and she had no trouble with micturition, menstruation or digestion. She had had no previous illnesses of significance.

On examination of the patient, her temperature was 98·8° F., her pulse rate was 84 per minute, and her respirations numbered 20 per minute. She was comfortable and her nutritional state was good. Examination of her chest revealed dulness to percussion on the right side, with diminished breath sounds, bronchial breathing and diminished vocal resonance; but complete general examination revealed no other abnormality.

A series of investigations were undertaken with the following results. X-ray examination of the chest revealed a dense rounded opaque area occupying most of the right half of the thorax, with some clear lung at both the base and the apex. The responses to the Casoni test and the hydatid complement fixation test were negative. A plain X-ray picture of the abdomen and the liver revealed no abnormality.

A complete blood examination on January 28, 1949, gave the following information. The erythrocytes numbered 4,800,000 per cubic millimetre, and the hæmoglobin value was 13·3 grammes per 100 millilitres of blood (86% Sahli); the average diameter of the red cells was normal, the relative volume of packed red cells was 42%, the mean corpuscular volume was 87 cubic $\mu$, the average corpuscular hæmoglobin was 28$\gamma\gamma$, and platelets were plentiful. The leucocytes numbered 7300 per cubic millimetre, 55% being polymorphonuclear cells, 33% lymphocytes, 7% monocytes and 5% eosinophile cells. The red cells were normal.

Excretion urography revealed that both kidneys were normal.

In view of the findings it was decided to perform an exploratory thoracotomy. This was carried out on February 11, 1949, under cyclopropane anæsthesia administered by Dr. S. Hecker. A longitudinal incision was made, centring over the upper part of the axilla over what was taken to be the fifth rib. The anterior portion of the rib extending from about three inches behind the costochondral junction to the anterior end of the cartilage was removed. The pleura was then opened. The mass was inspected and a suture was then run to attach a layer of tissue, which was peeled off the cyst wall. After this had been slit off, an incision was made into the cyst, the contents of which were then sucked out. Two masses were removed from the postero-lateral aspect of the interior of the cyst, one being about the size of a turkey's egg and the other the size of a fowl's egg, of an irregular shape with a rather woolly surface. The pedicles of these were tied off with number 2 size silk. After the whole of the visible contents as far as possible had been cleared out of the cyst, the opening in it was sutured with number two catgut, a small glove drain being inserted down to the incision in the pleura. The skin was closed with interrupted silkworm gut and silk sutures.

It was decided to close the chest and reopen it at a later date to deal with the condition at leisure. This was done a week later, on February 18, with the following result. A long incision was made overlying and parallel to what was regarded as the seventh rib. This was carried down to the

rib, which was then excised from its angle to the costal cartilage. The rib bed was incised and an attempt was made to open the pleural cavity. It was found almost impossible to gain entry to the pleural cavity, as the cyst was in contact with the rib bed throughout its length. By blunt dissection, aided by occasional sharp dissection, the surface of the cyst was ultimately defined; then by persistence of blunt dissection, occasionally aided by the cutting of thick bands of supporting tissue, the cyst was gradually dissected all round. When ultimately the majority of it had been separated from its surroundings, its extent was found to be enormous, as it extended almost to the dome of the pleura; it occupied practically the whole of the front of the thoracic cavity, posteriorly almost filling the thoracic cavity—the lung appeared as a collapsed carnified body in the posterior aspect of the thorax. Great difficulty was experienced in separating the cyst, particularly posteriorly and inferiorly. It was stripped out of the anterior mediastinum quite easily, as it was supported only by loose fatty tissue in that position. But posteriorly, superiorly and inferiorly, it was solidly attached to the neighbouring structures, these being in its posterior aspect the *vena cava* and vessels supplying the lung, superiorly the great veins in the neighbourhood, and antero-inferiorly the pericardium. On account of the danger of approaching the great veins, it was found necessary ultimately to cut away most of the cyst, a small portion only at its base being left attached to the structures, the veins, and the pericardium. This gave more room for the proper approach to the remnant, and by combination of blunt dissection and cutting with a knife the cyst was ultimately freed entirely from its attachments and removed. At one point the inferior *vena cava* was almost opened. Hæmostasis was secured by diathermy and ligatures where indicated. Penicillin, "Monacrin" and sulphanilamide powder were placed inside the cavity, and a tube was let out from its antero-lateral aspect after a small piece, about one inch, of the next lower rib had been removed. The wound was closed by continuous number 2 catgut sutures in the intercostal tissues, by interrupted and continuous sutures in the muscle layers, and by interrupted silkworm gut sutures in the skin.

The patient's convalescence was uneventful, and she was discharged from hospital, well, on March 12, 1949.

Reports on the specimens submitted to Dr. J. O. Poynton, of the Institute of Medical and Veterinary Science, are as follows. On February 14, 1949, the dermoid cyst of the lung was pathologically examined. Examination of a section showed the cyst to be a dermoid cyst lined by squamous epithelium. The wall was rich in sebaceous glands. There was no evidence of malignancy. On February 22, 1949, the dermoid cyst of the mediastinum was examined. Macroscopic and microscopic examination confirmed the tumour as a simple dermoid cyst containing epithelium, sebaceous glands, cartilage, fat, muscle *et cetera*. The specimen was handed to the Department of Pathology for suitable preservation.

The patient reported last towards the end of 1950, when she expressed herself as feeling well. X-ray examination revealed no evidence of recurrence, and the lung had expanded to fill the right half of the thoracic cavity.

## Reviews.

**Histochemistry: Theoretical and Applied.** By A. G. Everson Pearse, M.A., M.D. (Cambridge), D.C.P. (London); 1953. London: J. and A. Churchill, Limited. 9¼″ × 6½″, pp. 538, with 109 illustrations and four plates in colour. Price: 60s.

THE application of chemical and physical procedures to tissue sections for the determination of the presence of and site of different substances inside and outside cells has long been practised, but there has not been available any exhaustive and critical account of the various procedures. This want is now adequately filled by A. G. Everson Pearse's book. Practically every method which has been found useful is described in detail and a critical appraisal of the value of the procedure is given. It is obvious that the author has himself used most of the methods. A feature of the book is the excellent illustrations, many of them in colour. The theoretical background of the various tests is discussed in detail, indeed almost too much detail. Some of the chemistry is rather overdone for a book of this kind. For example, elaborate constitutional formulæ for different dyestuffs seem to be unnecessary. After a good section on the chemistry of fixation of tissues there are detailed methods for the investigation of proteins and amino-acids, nucleoproteins, carbohydrates, lipids and lipoproteins, aldehydes and ketones, alkaline phosphatases, acid phosphatases, other esterases, oxidases and dehydrogenases, pigments and inorganic constituents, and a short account of physical methods. There are also seventeen appendices giving details of the different methods recommended. This is a most useful book for anyone who has to deal with tissue sections whether in histological and biochemical research or in the examination of pathological tissues.

**The 1952 Year Book of the Eye, Ear, Nose and Throat (October, 1951-September, 1952).** The Eye, edited by Derrick Vail, B.A., M.D., D.Oph. (Oxon.), F.A.C.S., F.R.C.S. (Hon.); The Ear, Nose and Throat, edited by John R. Lindsay, M.D.; 1953. Chicago: The Year Book Publishers, Incorporated. 8″ × 5½″, pp. 456, with 120 illustrations. Price: $6.00.

THE highlight of the section on the eye, which takes up the first half of this volume, is a survey of retrolental fibroplasia by Leona Zacharias. This survey, originally published in October, 1952, is reprinted here in modified form, but it still provides a comprehensive picture of current knowledge and speculation on a baffling modern problem of ophthalmology and pædiatrics. The rest of this section is divided into chapters on the orbit and adnexa, the conjunctiva and cornea, the uvea, the lens and cataract, refraction and motility, the optic nerve, neurology and visual fields, the retina, glaucoma, surgery, therapy and miscellaneous subjects.

In the second part of the volume the subsection on the ear opens with a long chapter on hearing and hearing tests; this covers the literature on both experimental and clinical observations. Then follow chapters on vertigo, deafness and Ménière's disease, on Eustachian tubal function and *otitis media*, on otosclerosis and fenestration, on facial paralysis, on the parotid gland and on miscellaneous subjects. In the subsection on the nose and throat the material is grouped into chapters on an anatomical basis with extra chapters on allergy and on miscellaneous subjects.

The volume covers journals received by the editors between October, 1951, and September, 1952. It will keep the specialist informed on what is being written on his subject in general medical literature as well as in his special journals. Those practising in general or other special fields will find it a comprehensive guide to current views in two important specialties.

**Physical Diagnosis.** By Harry Walker, M.D., F.A.C.P.; 1952. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical) Proprietary, Limited. 10″ × 7″, pp. 462, with 126 illustrations. Price: £4 4s.

DR. WALKER is assisted by six other contributors in the preparation of this new book on physical signs. Dr. Walker points out that physical signs as an aid to diagnosis have not been replaced by laboratory and other scientific forms of investigation, but rather strengthened by these and placed on a firmer foundation. Some physical signs have also been found to be of little use and are consequently omitted.

The book is divided into three sections: "Physical Diagnosis", "Diseases of the Respiratory System", and "Diseases of the Circulatory System". Why these two systems are selected for further detailed consideration and correlation is not quite understood in a book whose title implies that it is not aiming to be a text-book of medicine. The section on physical diagnosis deals with the body in various sections from the head to the neck, upper extremities, thorax, abdomen, lower extremities, and then, departing from this plan, deals with the nervous system separately. This whole arrangement seems to be unfortunate, as the student of medicine usually prefers to learn physical examination system by system. He will find it difficult to integrate the cardio-vascular system when the veins of the neck are described in one chapter, the radial pulse in another, the liver in a third chapter, and examination of precordium in yet another. Whilst it is possible for the experienced clinician to examine a patient in this way and to integrate the various systems, this approach to physical examination would be most confusing to an undergraduate in medicine.

The latter would also find the bald statements of fact, without much anatomical or physiological basis, difficult to follow.

We are critical of the method suggested for recording the physical examination given on page 25 where the findings are recorded in spaces provided under various anatomical parts of the body. Whilst the list is reasonably complete for most systems, the nervous system seems to be represented by little more than all the known reflexes.

The following inaccuracies will be quoted: Page 48: "Ptosis of the upper lid is due to paralysis of the oculomotor nerve. When unilateral, Horner's syndrome . . ." Page 81: Clubbed fingers—no mention is made of carcinoma of the lung as a cause of clubbed fingers.

On the whole the book is not well illustrated for one aiming at teaching physical examination. We cannot recommend this book to medical students being taught by the usual British methods.

**Gynecological and Obstetrical Pathology.** By Peter A. Herbut, M.D.; 1953. Philadelphia: Lea and Febiger. Sydney: Angus and Robertson, Limited. 9½" x 6½", pp. 684, with 428 illustrations and two plates in colour. Price: £6 14s. 3d.

THIS is a new book, designed, according to the preface, for anyone interested in the female generative system. It is presented from the regional point of view and each subject is prefaced by introductory chapters on embryology, anatomy and physiology. The clinical viewpoint prevails throughout and this is as it should be, for pathology is only one aspect of disease. Consequently, each subject has such headings as "Clinico-Pathologic Correlation", "Diagnosis", "Treatment" and "Prognosis".

The book is both concise and comprehensive; consequently there is a very large number of references and seldom any indication as to which are worth reading in the original.

There is a tendency to quote from established authors in an uncritical manner. This is how errors become traditional from book to book. For instance, in discussing precocious puberty, the author states that most are examples of "constitutional precocious puberty", and he quotes from Novak the case of the Peruvian child who became pregnant at the age of five years eight months. Presumably the reference is to Lena Medina, who was a classical example of Albright's disease having the bony changes and pigmentation in addition to the precocious puberty (Wiener, K. (1947), "Skin Manifestations of Internal Disorders", The C. V. Mosby Company, St. Louis, page 413).

Figure 66, which purports to be a primary melanoblastoma of the vagina, is more probably a secondary growth. Furthermore, it is not "the consensus at present that the dermal nerve endings serve as points of origin" (of nævi), as stated in the chapter on the vulva.

There are two chapters at the end of the book contributed by L. A. Erf, M.D. The first deals with blood groups and the second with anæmias of pregnancy. These are clearly presented, and especially in the case of the chapter on blood groups, are good basic introductions to these subjects.

In general the material is well presented in a concise fashion, well written and well illustrated. Minor adverse criticisms should not discourage anyone purchasing this volume who is undeterred by the price.

**Local Analgesia: Abdominal Surgery.** By R. R. Macintosh, M.A., D.M., F.R.C.S. (Edin.), D.A., M.D. (hon. causa), Buenos Aires, and R. Bryce-Smith, M.A., B.M., B.Ch., D.A.; 1953. Edinburgh and London: E. and S. Livingstone, Limited. 9" x 6", pp. 94, with 88 illustrations. Price: 22s. 6d.

THIS is a beautifully produced little book. The many anatomical illustrations, most of them in colour, will satisfy the artist, and, for the most part, the anatomist. But the posterior margins of the external and internal oblique muscles are shown deep to the sacro-spinalis in Figure 12, and the intercostal nerves are showed bending sharply forwards as they enter the posterior surface of the rectus muscle.

Apart from strangulated hernia, no mention is made of that most common and pressing emergency, in which local anæsthesia finds a most useful place, namely, an advanced stage of acute intestinal obstruction with copious vomiting. A caecostomy or colostomy, under local anæsthesia by infiltration of the abdominal wall, layer by layer, is often a life-saving measure which can easily be applied, even by those who have not had special training in local anæsthesia. Nor is mention made of the usefulness of local anæsthesia in at least the early stages of some gastric operations, in order to ensure the emptying of the stomach. These omissions are curious in view of the recent report submitted to the Association of Anæsthetists on anæsthetic deaths due to regurgitation.

Splanchnic anæsthesia by the posterior method is described, but no mention is made of the anterior route. This is unfortunate, because many years ago, those with the widest experience in local anæsthesia for abdominal surgery, such as Finsterer and Kirschner, abandoned the former route because of its dangers, and retained and improved the anterior method.

Lastly, no mention is made of injection practice on the cadaver with methylene blue, which should be a part of the tiro's training.

## Notes on Books, Current Journals and New Appliances.

**Family Doctor.** Published monthly by the proprietors, the British Medical Association, Tavistock Square, London, E.C.1. Sole agents for Australia and New Zealand, Gordon and Gotch (Australia), Limited. Subscription for twelve months: 20s. (sterling), including postage.

THE June issue of *Family Doctor* is gaily decked out for the coronation with appropriate emphasis on the Royal example in home and family life. In special articles for the occasion Sir Zachary Cope tells of "Queen Elizabeth I and Her Doctors", Dr. T. Traherne writes on "The Queen and Her People", Dr. William Brockbank gives an account of "The Queen's Touch", and Pat Sullivan describes delectable food for coronation parties. A charming centre-piece deals pictorially with the "Childhood of Royalty". Other articles tell of a small girl's successful rehabilitation after poliomyelitis, the factors determining sex at conception, the dispensing of a prescription, keeping toddlers safe from tablets, eczema, relaxing for health, summer diet, rewards and punishments for children, adoption, and the usual features. We like the picture of Rosemary and her new brother. It is not surprising that *Family Doctor* is now well established in popular favour.

## Books Received.

[*The mention of a book in this column does not imply that no review will appear in a subsequent issue.*]

"The Anatomy of the Nervous System: Its Development and Function", by Stephen Walter Ranson, M.D., Ph.D., revised by Sam Lillard Clark, M.D., Ph.D.; Ninth Edition; 1953. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 7", pp. 594, with 434 illustrations, 18 in colour. Price: £4 0s. 9d.

In this revision of the text an attempt has been made to blend the account of structure with function to aid the understanding of the student.

"Biochemistry in Relation to Medicine", by C. W. Carter, M.A., B.M., B.Ch., and R. H. S. Thompson, M.A., B.Sc., D.M.; Second Edition; 1953. London: Longmans, Green and Company. Melbourne: Longmans, Green and Company. 9" x 6", pp. 536, with 36 text figures. Price: 52s. 6d.

The first edition was published in 1949.

"A Manual of Clinical Allergy", by John M. Sheldon, M.D., Robert G. Lovell, M.D., and Kenneth P. Mathews, M.D.; 1953. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 6½", pp. 428, with 27 illustrations. Price: £4 0s. 9d.

Intended primarily for the physician interested in devoting part of his time to the treatment of allergy patients or in establishing an allergy practice.

"The Government and the People, 1939-1941", by Paul Hasluck; 1952. Canberra: Australian War Memorial. Sydney: Angus and Robertson, Limited. 9½" x 6½", pp. 662, with 72 illustrations. Price: 25s.

This is the first of two volumes dealing with the political and social events in Australia during the Second World War. It deals with the period preceding the entry of Japan into the war.

The Medical Journal of Australia

SATURDAY, JUNE 27, 1953.

*All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.*

*References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: surname of author, initials of author, year, full title of article, name of journal without abbreviation, volume, number of first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.*

*Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.*

## MANNERS.

> Manners must adorn knowledge, and smooth its way through the world. Like a great rough diamond, it may do very well in a closet by way of curiosity, and also for its intrinsic value; but it will never be worn nor shine, if it is not polished.

THESE words were written by Chesterfield in 1748 and may well serve as a basis for a discussion on manners. Such a discussion seems to be called for today more than ever before because lack of manners is becoming more and more evident in all circles of society, professional as well as lay. The cynic may say: "Why bother about a discussion? Few who should read it will bother, and if they did, would take no notice." If we adopted this attitude we should never attempt by the written word to correct any fault or bring about any change. Some people seem to think that manners are something to be displayed or, shall we say, put on, like a suit of clothes for a special occasion and to be discarded when the event has passed. On a previous occasion we stated that manners are born of education out of understanding and good will and that they bespeak a respect for the feelings and comfort of other people. They are indeed the oil that will make the wheels of social intercourse run smoothly. Either, therefore, manners are part of a man's normal equipment or they are not. No man willingly runs the oil out of the sump of his motor-car's engine when it is running smoothly; he may in an absent-minded moment forget to replenish his supply of oil, but he will pay for his neglect in the damage done to his engine. The social sump is much like this. And this reminds us that some wheels, even in the social world, are of such high quality and are bathed in such superior oil that the unit is, as it were, hermetically sealed and needs no refilling. These are rare.

In the medical world, when we think of manners we think chiefly of professional manners or what is known as medical etiquette. (The laity need to be constantly reminded that medical etiquette is distinct from medical ethics—one is a question of manners, the other of morals.) But whether we think of medical or everyday manners, we must, to gain a proper conception of them, remember how manners are acquired. A baby is not born with good manners—it is a healthy little animal and does exactly what any other healthy young animal would do unless it is submitted to restraint and training. Children are quick to learn if they are properly taught, and in the teaching of them it is important to remember that example is better than precept. One cannot expect a child to display good manners if the parent lacks them. Moreover, if the parent expects a child to be polite and good mannered to him he must be polite and good mannered to the child. This is all summed up in a statement discussed on a previous occasion in these columns: "Even Children are People." Many a parent destroys the confidence of a child and alienates his affection by an over-insistence that the parent must always be right and by a failure to gain the understanding of the child. The result is a lack of friendship between parent and child, and friendship, we must remember, is the basis of every happy relationship in the home. These considerations of manners and the child have their counterpart when we think of professional relationships. Medical students coming fresh to the clinical years of their course make their first acquaintance with the patient-doctor relationship and they are not slow to realize that there is an important relationship between one practitioner of medicine and another. They gain their knowledge of medical matters from their seniors—their teachers—and passing into practice, they are set an example of good manners or lack of them by their seniors. The young graduate who has acquired good manners in his childhood will be "conditioned" to correct medical etiquette, but he will not be an example of correct social behaviour if those who have become practitioners before him treat him in a vulgar and selfish fashion. As the parent in this matter is to the child, so is the senior practitioner to the junior. The senior practitioner would like the junior to respect him and possibly to treat him with deference, as many a parent expects similar treatment by a child. Both senior and parent have to remember that respect must be earned. It is the quality or virtue in a man that wins respect, not his antiquity. We may admire a medical man's erudition and envy his insight, but if his manner to patients is crude and repulsive we cannot respect him. Such a man acting as a teacher (it has been known to happen in an Australian hospital) is likely to have a bad effect on a student at his most susceptible period—Saint Paul knew this when he wrote that "evil communications corrupt good manners". Unfortunately it is easier to break down than to build up habits, and a display of good manners would probably have no effect on a "rough neck".

Several matters may be mentioned in which the cultivation of good manners by members of the medical profession would make life a little pleasanter than it is. The first has to do with the courtesy that should be shown by doctors who take up practice in a district either by buying a practice or by "squatting". Tradition and decency demand that the newcomer shall pay a formal visit to others already practising in the district. Nowadays this courtesy is often omitted—the omission is surely not through ignorance, but from lack of manners. It is also painfully true that the older resident who does receive the formal visit does not always return the call. Both practitioners are at fault. The younger forgets that he will some day possibly be known as "the old fellow down the

street" and may then resent cavalier treatment of the kind that he now indulges in; the older fails in his obligation to the younger man, setting a permanent barrier between them and encouraging a wilful neglect of good manners. Stress has been laid on the duties and failures of the younger men; the seniors must also take heed. Consultants are not necessarily seniors, but they assume or are given a kind of superior status and thus have special obligations. It is, or should be, customary for a consultant to communicate with a practitioner who has sent a patient to him for an opinion or for treatment. The letter to the referring practitioner is not always sent and the consultant gives the impression that he is determined at all costs to keep the patient as his. No doctor has proprietary rights in any patient. Certain methods of procedure are recognized as correct when a patient is sent from one doctor to another or when consultations take place between two or more doctors about a patient. Not the least of these is the courteous acknowledgement that a patient sent has arrived and that something can or cannot be done for him.

Many other aspects of manners in the professional and social spheres could be mentioned. One can think of the lack of manners displayed by smokers of tobacco—in medical conclaves where addicts entirely disregard the comfort and even the well-being of non-smokers, and at the public and private dinner table, where smokers with complete selfishness spoil the meal of non-smokers, without a "by your leave" or any other apology, in order to satisfy their craving. This is a common phenomenon at medical dinners where the loyal toast is honoured half-way through the meal at the instance of a feeble or thoughtless chairman. One can think, too, of manners in the hospital ward, where the big "honorary" is treated almost like an Olympic deity and sometimes behaves like one, to the humiliation of the nursing staff. When this happens, the "evil communication" does "corrupt" lesser members of honorary and resident staffs. It is not necessary to refer to other spheres in which manners have deteriorated, though perhaps passing mention may be made of the contribution that is possible by medical practitioners to courtesy in the driving of motor vehicles and in the use of telephones.

The question will be asked, what can be done about a reappearance of good manners in professional and social life? Quite often forgetfulness or want of thought is to blame for our lapses. The remedy thus lies with each individual. It is true that "one may smile, and smile, and be a villain", but manners are to a certain extent a reflection of underlying character. We started with a quotation from Chesterfield; we may conclude with one from Bacon:

> Behaviour seemeth to me as a garment of the mind, and to have the conditions of a garment. For it ought to be made in fashion; it ought not to be too curious; it ought to be shaped so as to set forth any good making of the mind, and hide any deformity; and above all, it ought not to be too strait, or restrained for exercise or motion.

# Current Comment.

## INHALATION THERAPY IN PERNICIOUS ANÆMIA.

THE introduction of the simpler forms of parenteral therapy was a great forward step when its advantages reached the patient suffering from severe pain, as morphine has been one of the outstanding drugs requiring use by injection to give its maximum effect. Since then the number of therapeutic substances most effectively employed by subcutaneous injection or by introduction into the circulation direct has steadily increased, and other routes have been used, such as the intrathecal and intraabdominal. The choice of a route for the administration of morphine is a good example of the contrasted advantages and disadvantages; the oral route is the easiest and does not need a skilled third party, but it is ineffective; the sublingual is as simple, but little better; the subcutaneous is the best routine method, while the intravenous, by reason of its speed and effectiveness, resembles brief general anæsthesia. The difference is simply a question of the speed and thoroughness with which the drug reaches the general circulation. The great value of the use of vitamin $B_{12}$ in pernicious anæmia is that this substance is highly concentrated and calls for but a small bulk, and it is also therapeutically very active. There is, however, the drawback that it does not give the characteristic response unless given by a parenteral route, and in a lifelong disease there is always the risk that the patient may grow weary in well-doing and slacken in his attendance on his physician. Ingenuity has now suggested another method, by which one of the large capillary beds of the body may be utilized to absorb crystalline vitamin $B_{12}$ without puncture of the skin. Raymond W. Monto, John W. Rebuck and Michael J. Brennan, in an account of their experience with an inhalational method, point out that good absorption should be obtained through the wealth of blood and lymphatic vessels in the air passages.[1] Success has been gained in other therapeutic fields with such substances as antibiotics, hormones and vasoconstrictors, and now the present authors record good results in the treatment of pernicious anæmia. The first two patients in this small but well-studied series were treated by a solution of crystalline vitamin $B_{12}$ in physiological saline without preservative, and an aerosol of this solution was used in a nebulizer activated by a pressure tank. In order to permit the patient to use the method himself, a hand atomizer was employed later with equally good results. The third patient was treated by a dust composed of the crystalline active agent intimately mixed with lactose powder. The volume used was only 0·1 cubic centimetre, one-tenth of the bulk of the aerosol used previously. A special commercial dust inhaler was used by the patient, who was instructed to take ten deep breaths with each administration. The authors found later that more of the active material reached the absorbent area if the patient exhaled strongly, then took a slow deep breath, held it for a few moments and then exhaled again through the nose. The response was excellent in all patients, and no other method than the inhalatory was used. Full investigation of these patients left no doubt that the picture in the blood films and in material aspirated from the bone marrow was that characteristic of pernicious anæmia. Reticulocyte response reached 21% on the seventh day, and on the eighth day of treatment 44% in the first patient, and in the others satisfactory increases also occurred. The general improvement was noteworthy in all, and it was found that good response could be obtained in patients who had in two instances a severe form of the disease and a mild form in one. The authors found no sign of irritation or other toxic effect in either technique employed, and were able to entrust the administration to the patients, who after the initial daily intensive period were controlled by three treatments per week. Tests of the urine showed that detectable amounts of vitamin $B_{12}$ could be demonstrated after respiratory administration. Three more patients have since been treated for relapse of pernicious anæmia not previously treated by inhalation. The dosage levels found effective were below that required by oral methods. Nevertheless the authors admit that some additional oral or parenteral dosage is necessary as well as the inhalation of vitamin $B_{12}$.

It will be seen that even in so small a series it has been demonstrated that inhalation is to a reasonable extent effective, but surely parenteral therapy has pride of place. We may recall that deep inhalation of adrenaline is effective to a fair extent in asthma, but injection is more useful and practical, except where it is not readily practicable for the

[1] *Am. J. M. Sc.*, February, 1953.

patient to depend on someone who can give hypodermic injections. It might be that self-administration of vitamin $B_{12}$ might be occasionally permitted where the circumstances suggest it. This is all with a proviso, that further investigation substantiates this work. It is at least of physiological interest.

## INFECTIVE HEPATITIS.

UNDER a variety of names infective hepatitis has been known for a long time. It is a virus disease with damage to liver cells which may be severe enough to cause death with acute yellow atrophy or so mild as to be not noticed, often, but not always, associated with jaundice. From time to time when a large number of persons are injected with human blood serum or plasma a large percentage of them develop infective hepatitis. The same event sometimes follows injections of some vaccine, such as yellow fever vaccine. Persons infected by serum injections may infect contacts in a manner at present uncertain. In institutions in which large numbers of children or adults are congregated infective hepatitis has often been endemic. In the *Transactions of the Eleventh Conference on Liver Injury*, sponsored by the Josiah Macy Junior Foundation, there is a large section dealing with infective hepatitis. Thirty more or less distinguished physicians, surgeons, pathologists and others interested in liver function and liver disorders took part in the discussion. As there were no set lectures, but only statements, questions, answers and comments by the various speakers, it is difficult to pick out a connected story, but some important points were brought out. In an investigation on the value of influenza vaccine as a prophylactic 1017 persons were each given influenza vaccine and 750 others an equal volume of control material containing 0·03 millilitre of pooled human plasma. Two hundred and seventy-three cases of hepatitis developed in the group which received the plasma and 27 cases in persons who did not receive plasma injections. The incubation period following plasma injection varied from 43 to 125 days and averaged 79 days. In the 27 cases the sufferers were apparently infected from the others. About one-fifth of all the patients were non-icteric. More than half of the patients had some allergic manifestations.

Another outbreak of a different character was studied in a Chicago orphanage. Here, since 1942, hepatitis has been endemic, but only one of the children between 1942 and 1948 had jaundice. Between 1946 and 1948, of 139 nurses 44 had jaundice. Gamma globulin injections were found to be highly protective to a new batch of nurses. The source of the infection was traced to two children who were excreting the virus in their fæces. More adequate precautions in the handling of the children were introduced and there have been no new cases of hepatitis since the beginning of 1950. This endemic disease had an incubation period of thirty days in contrast with the average of seventy-nine days in the first series. An important point is that as little as 0·01 millilitre per pound of body weight is highly protective against infection with this type of hepatitis. From this and other parallel studies there is evidence that with $\gamma$ globulin and exposure to infection there is developed a passive-active immunization. It is important, to distinguish between chronic epidemic hepatitis (IH virus) as seen in the Chicago orphanage and chronic active serum hepatitis (SH virus). In the first type the infection is carried in the stools. In the second type, although a number of carriers is now known, careful experiments with human volunteers have shown that the virus apparently is absent from the stools. There is a lack of cross-immunity between the strains of IH virus and SH virus, and it seems clear that these viruses have marked antigenic differences.

The existence of chronic carriers of the SH virus, several of whom have given no history of jaundice, raises a serious problem in relation to blood transfusion. In the United States there are more and more cases of post-transfusion jaundice, suggesting that more of the blood donors are carriers of the virus. Another important point is the possibility of carrying the virus from carriers to healthy persons by needles, syringes and knife blades not sterilized by heat between the injection of patients. In a twelve-year period at the Johns Hopkins Hospital it was found that one out of every seven patients admitted to hospital with acute hepatitis had been transfused with homologous blood or a blood fraction five weeks to five months before the onset of hepatitis. Moreover, 20% of 183 patients with hepatitis had had a parenteral test or injection of material, other than blood or arsenic, within five weeks to five months before the onset of their illness. It was concluded that this was definite evidence that the casual needle prick did account for a good number of cases of hepatitis. Individually sterilized needles and knife-blades are now being used exclusively at Johns Hopkins Hospital even for blood counts. Dentists also probably disseminate hepatitis. It is pointed out that the cost of a thousand needles is far less than the cost of treatment in hospital of one patient with serum hepatitis for four weeks or longer. Several speakers mentioned the value of glass chips for puncturing the skin for blood counts.

## THE DIAGNOSIS OF ACUTE MENINGITIS IN INFANCY.

IT is a commonplace now to say that the acute infections have been in large measure subdued as a result of developments in chemotherapy. The conquest of the bacterial infections is nearly complete. However, one weak link in the subduing chain has to be borne in mind; it is the problem of making an early accurate diagnosis, a problem that is at its greatest in infancy, when the consequences of misdiagnosis are most serious. A case in point is acute purulent meningitis. The prognosis for this condition in infancy has improved remarkably since the discovery and use of the sulphonamides and antibiotics, but J. C. Haworth[1] quotes figures to show that the fatality rate in this age group is still alarmingly high. He considers that one of the factors causing this high rate is delay in diagnosis. The classical clinical features are often absent in this group during the early stages of the disease, or they may appear at a time when treatment is no longer effective; the fact that experienced pædiatricians may be able to detect subtle early signs does not alter the practical situation a great deal. Haworth illustrates not only the difficulties of diagnosis, but also their serious consequences from an analysis of 50 case records of infants with acute meningitis at the Alder Hey Children's Hospital in Liverpool. Of the 50 infants, 13 had none of the "classical" signs of meningitis, and seven of these 13 children died; in five of the seven fatal cases the diagnosis was made *post mortem*. It is notable that the total number of deaths in the whole group of 50 was only 11. An incidental but important point brought out in this analysis is that, in infants with meningitis, convulsions are of grave prognostic significance. Prophylactic anticonvulsant drugs had not been used as a routine, and Haworth makes a plea that they should be so used. However, the importance of delayed diagnosis in keeping up the fatality rate remains clear. Haworth quotes the statement of H. E. Alexander that stiffness of the neck and Kernig's sign are highly unreliable in the first few months of life and seldom appear before the advanced stage of meningitis. Alexander considers that more useful signs in the diagnosis of meningitis in infants aged less than seven months are drowsiness alternating with irritability, a high-pitched cry and a vacant look in the eyes. In view of this Haworth recommends that lumbar puncture should be performed on any infant in the following circumstances: the child is unusually drowsy or irritable, or has a "vacant look" in the eyes or a recent squint; the child's illness is more than can be explained by the physical signs; the expected response is not obtained to treatment for a disease such as pneumonia or gastro-enteritis. It certainly seems unwise to depend on the presence of "classical" signs and symptoms.

[1] *Lancet*, May 9, 1953.

# Abstracts from Medical Literature.

## MEDICINE.

### Risks of Blood Transfusion.

BERNARD STRAUS AND JOSE M. TORRES (*J.A.M.A.*, February, 1953) emphasize the risks of blood transfusion. They state that of 100 consecutive patients who received blood, 399 bottles in all, ten had transfusion reactions and one died. There were three cases of homologous serum jaundice. Half the reactions occurred in patients given blood for inadequate reasons.

### Benign Prolapse of Gastric Mucosa.

JACOB LICHSTEIN AND LEONARD M. ASHER (*J.A.M.A.*, February, 1953) give an account of the ætiology, clinical features, diagnosis and treatment of benign prolapse of gastric mucosa into the pylorus from their series of 52 cases. They state that recognition of these cases is increasing nowadays. The diagnosis is made by X-ray and gastroscopic examination. The commonest complaint is repeated bouts of epigastric pain with dyspepsia, not relieved by food. Treatment may require surgery.

### Pyridoxine and Mercurial Diuretics.

S. WALDMAN AND L. PELNER (*Am. J. Med. Sc.*, January, 1953) found that pyridoxine restored the diuretic response to mercurials in ten patients with congestive cardiac failure who had become resistant to mercurials even when combined with vitamin *C*, ammonium chloride, aminophylline or lipoadrenal cortical extract. The patients were not salt-deficient. The mode of action of pyridoxine is not known. The dose was 100 milligrammes included in the injection of the mercurial.

### Cholangiolitic Biliary Cirrhosis.

W. E. RICKETTS AND R. W. WISSLER (*Ann. Int. Med.*, May, 1952) report a series of nine cases of cholangiolitic biliary cirrhosis, analysed with respect to the clinical, electrophoretic and pathological findings. The authors consider that the disease falls clinically into the following two forms: (*a*) Xanthomatous biliary cirrhosis, with insidious onset, jaundice, pruritus and persistent hyperlipæmia. In the authors' series there was no loss of weight or fever, and both cases occurred in women. (*b*) Non-xanthomatous cholangiolitic biliary cirrhosis, which is the biliary cirrhosis of Haust. In the authors' series it occurred in both sexes, there were often associated diseases, and fever and weight-loss were present in all cases. The biochemical findings, with the exception of the lipæmia, were the same in both groups. There was evidence of bile regurgitation with little or no alteration in hepatic function according to tests used. The authors state that the xanthomatosis is thought to be in part a primary condition because it occurs almost exclusively in adult females. It is, however, possibly also related to obstructive biliary disease with bile regurgitation. Only in cases with prolonged elevation of the serum lipids does xanthomatosis develop. Obstruction to bile tends to raise the cholesterol level, while acute biliary tract infection, malnutrition and parenchymatous liver disease tend to lower it. The ætiology is still controversial. There is no evidence that it is a parenchymatous liver disease or a condition secondary to parenchymatous liver disease. It is probable that the process is primarily an inflammation in and around the small bile canaliculi. There has been recent encouraging experience with chemotherapy.

### Boeck's Sarcoid.

O. REFVEM (*Acta tuberc. scandinav.*, Volume XXVII, 1952) observed that attenuated tubercle bacilli (B.C.G.) remained alive for four to five months in the skin of a patient suffering from Boeck's disease. He states that patients with this disease, whether reactors to tuberculin or not, should be carefully protected against exogenous infection with tubercle bacilli and that it is dangerous to treat them in tuberculosis sanatoria. Long-delayed but quite violent allergic reactions may follow tuberculosis infection.

### Disseminated Lupus Erythematosus.

M. A. SHEARN AND B. PIROFSKY (*Arch. Int. Med.*, December, 1952) discuss *lupus erythematosus* and present an analysis of 34 cases from the standpoint of clinical and laboratory features and response to therapy. Each case was diagnosed by suggestive clinical and laboratory findings, and confirmation of diagnosis was effected by the demonstration of the "L.E." cell, of pathological material, or of both. The age at onset in this series of cases varied from three to fifty-six years; and 19 of the patients were over thirty years of age. Of the 31 women, eight were outside the childbearing age. The predisposing factors are reviewed; preceding exposure to sunlight or ultraviolet rays was implicated in 18 of the 31 patients with skin lesions. Two patients had clinical tuberculosis, and two had *Actinomyces niger* infections. One patient suffered a remission following therapeutic abortion. Among those who died, the average duration of illness was found to be six years and four months, but a range of seven weeks to twenty years was encountered. The symptomatology in the series was varied and often bizarre; but all patients had fever, and 31 had skin lesions. A nephrotic state was present in four cases. Chronic non-suppurating parotitis was noted in three cases, and six patients had a history of a preceding skin eruption which was believed to be chronic discoid *lupus erythematosus*. Cardiac symptoms were present frequently, and congestive cardiac failure occurred in eight and hypertension in eleven cases. Systolic murmurs were common, and two patients with diastolic apical murmurs were found at necropsy to have had Libman-Sacks endocarditis. The electrocardiogram was considered abnormal in 21 of 29 cases. The sedimentation rate was elevated in all cases, and all but one patient had anæmia. Other abnormal laboratory findings included leucopenia in 74% of cases, an abnormal albumin-globulin ratio in 69%, proteinuria in 62%, hæmaturia in 35%, and a positive Wassermann reaction in 19%. Three patients clinically suspected of having hæmolytic anæmia yielded a positive result to the Coombs test. "L.E." cells were found in 29 of the 31 patients who were tested. "L.E." cells were regularly demonstrated when the patients were acutely ill; with improvement or remission the cells usually decreased in number and occasionally disappeared from the blood and marrow. Twenty of the patients received ACTH or cortisone, and the results were encouraging in the majority of cases. However, four patients died while receiving the hormones; two patients responded initially, but later became refractory to the treatment and died. In the case histories which are presented, some of the features of disseminated *lupus erythematosus* are illustrated, but because systemic manifestations so frequently precede the rash (in 41% in this series), the importance of a high index of suspicion is stressed.

### Prolapse of Gastric Mucosa.

FRANCIS W. WILSON AND LESLIE L. LEMAK (*Am. J. Digest. Dis.*, December, 1952) report five cases of prolapse of the gastric mucosa into the duodenum. The main symptoms were hæmorrhage or attacks of epigastric or chest pain related to the taking of food. In two cases, the condition was noted during healing of duodenal ulcers. The deformity was demonstrated by radiography, and in one case could be reduced by pressing on the upper part of the abdomen.

### Thrombocytopenic Purpura.

CHARLES C. SPRAGUE *et alii* (*J.A.M.A.*, November, 1952) uphold the theory that there is a factor in the plasma of patients with idiopathic thrombocytopenic purpura that destroys platelets. Blood from 14 of 16 such patients caused a marked and prolonged fall in platelet count when transfused into normal recipients. This effect was much greater than the transient depression of platelets caused by normal blood transfusions. The authors also marshal the evidence for the occurrence of isoimmunization to platelets in man, analogous to the mechanism involved in acquired hæmolytic anæmia. Transfusions with blood rich in platelets, such as from polycythæmic patients, were found to be of little use, whatever precautions were taken to preserve the platelets.

### Erythema Nodosum following Measles.

O. JENSEN (*Acta tuberc. scandinav.*, Volume XXVII, 1952) reports that after an epidemic of measles in Greenland two-thirds of a number of patients suffering from tuberculosis who had had measles had a secondary rise of temperature, and in one-half of these *erythema nodosum* developed.

### Diabetes Mellitus.

K. HALLAS-MØLLER *et alii* (*J.A.M.A.*, December 27, 1952) discuss the use of zinc insulin preparations in diabetes. They state that it is well known that some patients react well and others variably with these preparations. Crystalline protamine zinc insulin could give a slow prolonged action, a quick or a slow delayed action. In their investigation the average diet used was one of 1700 to 2000 Calories. The action of protamine zinc insulin or of the Danish insulins, iso-insulin and di-insulin (a mixture of insulin and phenylureidoinsulin), could give

reactions early in the afternoon or at night. Each patient was a problem in himself. The authors used insulins containing two milligrammes of zinc per 1000 units. The first insulin used was a suspension of amorphous precipitated insulin, the second a suspension of ground insulin crystals, and the third a suspension of insulin crystals of larger particle size, 0·01 to 0·02 millimetre. These three types gave an average activity of eighteen, twenty-four and thirty hours. If it was carefully used with different patients, it was found that an ideal insulin existed for all difficult cases. However, the difficulty of working out the results in each case was evident. The investigation is being continued.

### The Relief of Coronary Arterial Insufficiency.

C. P. BAILEY *et alii* (*J. Thoracic Surg.*, February, 1953) present a detailed review of an operation (Beck's operation modified) for delivering arterial blood to the ischæmic heart by reversing the flow through the coronary sinus and its ramifications. This is done by constructing an artificial communication between the aorta and the coronary sinus, a two-stage operation. Eighteen patients were operated upon: in two the operation was found technically impossible; two died after operation; one refused the second stage; in six the operation was unsatisfactorily performed by reason of thrombosis of the anastomosis or graft; in seven the operation was successful. The first patient treated had suffered three infarctions of the heart, took 100 tablets of nitroglycerin a week and could not walk fifty feet without pain; he was converted into a robust man who could easily run at top speed right round a city block.

### Tic Douloureux and Stilbamidine.

GEORGE W. SMITH *et alii* (*Ann. Int. Med.*, February, 1953) report a case of *tic douloureux* in an elderly patient with complete relief of symptoms by stilbamidine. They state that the effect is due to a late-appearing neuropathy of the fifth cranial nerves. The drug was administered intravenously once a day for fourteen days, at the end of which time symptomatic improvement commenced.

### Polyradiculitis Cervicalis Infectiosa.

J. STRÖM (*Acta méd. scandinav.*, Volume XXLIV, Fasciculus VI, 1953) discusses *polyradiculitis cervicalis infectiosa* or *myalgia nuchæ epidemica*. Seventy-two patients were studied suffering from pain in the occiput and neck, restricted movement and pain in the neck, fever, headache, nausea and vomiting. Epidemics of this kind have been described in the United States of America and Great Britain. Tenderness about the neck, trapezius and deltoid were observed. The condition lasted one to four days and tended to recur a week later. In the present report, contact with a previously affected patient was proved in 14%. An incubation period of one to eight days was apparent. Recurrence was not uncommon. The age of the affected person varied between three and seventy years, most being between twenty and fifty years. Numbness of the arms and paræsthesia was observed. The main clinical effect was pain in the back of the neck of great severity, associated with fixation of the head in a flexed position. Meningitis or poliomyelitis was usually suspected. The cerebro-spinal fluid was not consistently abnormal. Leucopenia was usual. The condition lasted from four to nineteen days. There was a resemblance to epidemic myalgia or Bornholm disease, though the location of the pain was quite distinct. Acute spondylitis, prolapsed intervertebral disk, acute cervical lymphadenitis, torticollis, meningitis and poliomyelitis may be suspected, as may various infectious diseases. Treatment was symptomatic; injection of 0·5% "Novocain" solution sometimes gave relief. The location of the lesion was difficult to determine; in considering this the author favours an irritation of the nerve roots, affecting either anterior or posterior nerve roots. The Guillain-Barré syndrome is compared, as well as similar syndromes with exclusively motor symptoms. The condition appears to be an infection due to a virus or a bacterium, the former being the more likely.

### Serum Iron Content and Hepatocellular Damage.

B. M. BATASSARIN AND M. H. DELP (*Am. J. Med. Sc.*, December, 1952) publish a study of 26 cases of liver disease in which full liver function tests were performed and the level of serum iron was investigated in each case. The serum iron values did not correlate with the results of any particular test of function, but closely followed the clinical course. The level was increased in the presence of hepatocellular damage and decreased as recovery took place. In the case of compensated cirrhosis in which little acute parenchymal damage is encountered, the values are normal. The authors think that the higher values associated with acute liver disease are due to disruption of the liver cells with release of iron.

### Intraarticular Cortisone Therapy.

A. S. DIXON *et alii* (*Clin. Sc.*, Volume XII, Number 1) describe the effects of intraarticular administration of cortisone and ACTH in cases of rheumatoid arthritis. Injection of 17-hydroxy, 11-desoxycorticosterone, compound E or cortisone into the knee joint in varying doses and solutions gave variable and unpredictable results. The absorption rate of cortisone acetate from the joint cavity could be as rapid as after intramuscular injection. Intraarticular injection of hydrocortisone acetate (compound F) produced greater biochemical and local clinical improvement than cortisone. These local effects were not as satisfactory as the improvement following general oral or intramuscular treatment. The test applied concerned the effect on the synovial fluid and synovial membrane. Examination of the fluid showed reversion to normal in all investigations.

### Lymphuria and Postural Proteinuria.

ERIC LÖWGREN (*Acta med. scandinav.*, December, 1952) in a preliminary report puts forward the theory that postural or orthostatic albuminuria may be due to the appearance of lymph from the renal lymphatic system in the urine. He suggests that this lymphuria is brought about by stasis in the renal lymphatics. Investigations based on this theory are in progress.

The same author (*ibidem*, January, 1953) reports a case of unilateral chyluria in which retrograde pyelography demonstrated the presence of communicating channels between the renal pelvis and its adjoining lymphatics. Trauma and infection are suggested as the cause of the condition.

### Unresolved Pneumonia Cleared with Streptodornase.

J. M. MILLER *et alii* (*Dis. Chest*, February, 1953) have effected the speedy resolution of slowly resolving pneumonia by instilling streptokinase-streptodornase through a bronchoscope into the affected part of the lung. They state that the treatment depends on the fact that the substance mainly responsible for the viscosity of the thick purulent exudate plugging the bronchioles is a nucleoprotein hydrolysed by streptodornase. It is advised that bronchoscopy be never omitted lest a bronchial carcinoma should be overlooked. It is possible that in some cases, when a carcinoma is present but undetected by bronchoscopy, the loosening of plugs of cellular debris from the bronchioles and the influx of serum, providing large quantities of sputum for direct examination for tumour cells, may lead to the diagnosis. The treatment is contraindicated in the presence of active pulmonary tuberculosis, as it may promote spread by the bronchi.

### Ocular Findings in Gout.

JOHN R. MCWILLIAMS (*Am. J. Ophth.*, December, 1952) reviews the ocular findings in gout and describes a case with conjunctival tophi. He states that gouty arthritic conjunctivitis has been described. Scleritis, a rare disease, is not infrequently associated with gout, and is often associated with tenonitis. In addition there may be episcleritis, which may be nodular or more frequently the so-called *episcleritis periodica fugax*. Tenonitis is always associated with episcleritis and is characterized by pain, proptosis and œdema. Iritis and keratitis have also been described. Tophi in the lids have been described, and the author describes a case in which conjunctival tophi were present.

### Intermittent Cardiospasm.

N. ASHERSON (*Brit. J. Tuberc. and Dis. Chest*, January, 1953) reports the case of a middle-aged man who had cardiospasm intermittently over a period of two and a half years. The only symptom was a feeling that food got stuck in the upper part of the neck, especially a piece of apple or dry bread. Ultimately a cancer of the cardiac end of the stomach was discovered. The author quotes Sir Heneage Ogilvie as saying that a diagnosis of cardiospasm should never be made in an adult with a short history until the possibility of a high gastric cancer has been excluded.

### Hyaluronidase and Renal Lithiasis.

A. J. BUTT *et alii* (*J.A.M.A.*, November 15, 1952) have noted that the subcutaneous injection of hyaluronidase increases the amount of protective urinary colloids and causes clearing of urine in patients who had previously had turbid urine with heavy sediment. They have applied this treatment to control stone reformation in patients who had previously formed stones quickly; results were favourable.

# Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

## LXVIII.

## HODGKIN'S DISEASE: DIAGNOSIS AND TREATMENT.

PATHOLOGICAL classification of lymphomatous tumours in general is admittedly a problem liable to involve considerable difficulty. The essential nature of lymphadenoma (Hodgkin's disease) is still somewhat obscure despite extensive clinical and pathological investigation in various countries. Current views of diagnosis and treatment form the basis of this communication.

In a study of a large series of lymphatic and hæmatopoietic tissues from cases of lymphomatous tumours carried out in the American Army Institute of Pathology during World War II, Custer and Bernhard (1948) recorded investigation of material from 700 cases of Hodgkin's disease. In the histological classification the terms paragranuloma, granuloma and sarcoma were used on the basis of predominating microscopic pattern. The authors concluded that rigid subclassification of lymphatic tumours of this nature was frequently impracticable, in that a striking fluidity might be observed in histological pattern and that the transitions and combinations in structure exhibited should be interpreted as indicating a single neoplastic entity having a number of variants.

In the classical picture, loss of normal architecture of gland tissue, increase of interstitial fibrous tissue in varying degree, Reed-Sternberg cells, twin mirrror-image cells and eosinophile cells are usually regarded as the significant features. Competent authorities maintain that the histological pattern of lymphoid tissues removed for biopsy from several glands in the same patient may show transitions and variations, thus adding further difficulty to exact pathological classification in a particular case. It may be that such variation of histological structure accounts for the extraordinary variability observed in the clinical course of the disease in individual patients in whom the diagnosis of Hodgkin's disease has been confirmed by microscopic examination of tissue.

The clinical diagnosis apart from tissue biopsy may be in certain instances fairly obvious; at other times it may present very great difficulty, particularly in cases in which the gravamen of the disease falls primarily upon mediastinal or abdominal lymph glands with or without early involvement of tissue in lungs, liver or spleen. In the classical type as described by Hodgkin in 1832, in which the patient presents with painless enlargement of glands usually in the cervical region without, as yet, severe constitutional disturbance, the peculiar "rubbery" consistency of the individual glandular masses, freedom from skin attachment and evidence of local inflammatory reaction may make the clinical picture quite characteristic. Considerable variation in the firmness and consistency, presumably determined by the degree of fibrous tissue hyperplasia in individual glands, may be a striking and significant feature. Apart from the classical clinical picture which is probably applicable to approximately 75% of cases, it is customary to recognize several other clinical types: (i) An acute form proceeding to rapid generalized spread with much constitutional disturbance. (ii) A localized form. (iii) Generalized lymphadenopathy. (iv) A mediastinal type with or without early lung involvement. (v) An abdominal form with or without recognizable involvement of spleen or liver. (vi) A splenomegalic form. (vii) An osteoperiostitic type. (viii) A gastro-intestinal type in which solitary or multiple tumours appear in the wall of stomach or intestine. (ix) A pulmonary type with early lung infiltration. There is, however, no hard and fast demarcation of several of these types: the morbid process having appeared primarily in a peripheral gland may gradually or rapidly become widespread.

Of particular diagnostic interest are those cases in which pyrexia is a pronounced feature, the most characteristic being the relapsing type described as the Pel-Ebstein phenomenon, in which enlargement of peripheral glands or spleen may be inconspicuous or absent in the early stages. In such cases an erroneous diagnosis of typhoid fever, tuberculosis or relapsing fever has sometimes obscured the issue.

Clinical diagnosis in the early phases of Hodgkin's disease may derive support from hæmatological investigation: in the earliest stages the blood picture may be normal; as the disease advances anæmia may be observed, usually of hypochromic normocytic type; neutrophile leucocytosis is frequent; lymphopenia is said to occur in 93% of cases; eosinophilia and monocytosis occur less constantly; immature white cells are found rarely. As the disease advances blood changes tend to increase. With extensive involvement of spleen and liver leucopenia may occur associated with hypoplasia of bone marrow. Blood platelets have been commonly recorded as numerous.

The clinical course of the disease is variable. Although apparent arrest of the morbid process has been observed following complete surgical extirpation or treatment by irradiation of an early localized group of glands, the course of the disease is usually progressive and characterized by further glandular enlargement, with asthenia and cachexia, which may be gradual or comparatively rapid in its course. Widespread or generalized pigmentation of skin is commonly observed and may become intense with advancing cachexia and emaciation. Pruritus may be a troublesome symptom occurring at any stage of the illness. In a disease so widespread in its ramifications topical symptoms obviously vary with the nature and situation of tissues involved; the anomaly and diffusion of clinical signs and symptoms may in some instances suggest the diagnosis in obscure cases.

### Treatment.

The present tendency is to regard irradiation as the appropriate primary method of attack, particularly when peripheral glandular enlargement is the conspicuous feature. Lack of further response or visceral involvement may render persistence in this procedure impracticable.

The recent introduction of nitrogen mustard ($HN_2$) and triethylene melamine (TEM) has added to therapeutic resources. Both these substances have been extensively employed in America and elsewhere, and various reports have appeared in the literature over the past four years. It is doubtful whether even yet a complete assessment of these chemical agents can be made. Most observations are in agreement that nitrogen mustard is capable of producing remissions of the disease over a variable period of time ranging from weeks to months and is useful for control of pruritus, fever and severe sweating; pain in cases of bone involvement is claimed to be materially lessened. More recently the introduction of triethylene melamine (TEM) has made treatment by oral administration possible. The clinical use of TEM has been critically reviewed by Kravitz, Diamond and Craven (1952). These observers conclude that the results which may be obtained with TEM in a patient suffering from Hodgkin's disease depend on the amount of active disease present, its aggressiveness, the presence of constitutional symptoms and the general condition of the patient. It is claimed that slight lymphadenopathy, fever, sweats and pruritus usually respond well initially to TEM. Efforts to maintain remissions in such patients with small doses at intervals may occasionally be rewarded by a prolonged symptom-free period. The authors maintain that partial response may be made by patients with advanced disease—decreased fever, sweats, itching and diminution of pain in the osteoperiostitic type with nerve root involvement. Successive daily doses of 2·5 to 5·0 milligrammes were advocated until a total of 10 to 15 milligrammes had been administered. The average total dose required to obtain remission was stated to be of the order of 35 milligrammes.

The use of TEM in lymphomatous diseases has recently been the subject of a careful review published in *Acta medica Scandinavica* (1952). It is maintained that nausea, vomiting and gastro-intestinal disturbances are of less severity after TEM administration than with nitrogen mustard. The margin of safety is, however, much narrower than that of nitrogen mustard in the individual sensitive to the drug. It is stated that profound and often irreversible marrow hypoplasia may follow doses as low as 10 milligrammes. This effect is stated as possibly occurring as early as the fourth day after administration or delayed as late as the eighteenth day. It would appear that the greatest danger in the administration of these drugs lies in the unpredictable vulnerability of the bone marrow. The narrow margin of safety in the sensitive individual precludes their use without meticulous attention to the state of the blood and marrow during and after the administration of the drug.

It would therefore appear that in the present state of knowledge the employment of chemotherapy should be limited to conditions under which adequate facilities for observation and hæmatological control are ensured.

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Sydney.

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# British Medical Association News.

## SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at the Hamilton Base Hospital, Hamilton, on March 28, 1953, DR. L. H. BALL, the President, in the chair. In the afternoon the meeting took the form of a series of clinical demonstrations by members of the medical and surgical staffs of the hospital.

### Ununited Fracture of the Femur.

DR. J. LE M. KNEEBONE presented a boy, aged twelve years, who had been involved in a motor-car accident in April, 1952, and could not walk for a week because of pain in the right leg. In September, 1952, he ran into a post, which he struck with his head, and was apparently stunned and fell to the ground. When he tried to get up, he found that he could not use his right leg, and he had to be carried home. Two days later, X-ray examination in Kaniva Hospital revealed a fracture of the neck of the right femur. A double plaster spica was applied to include the right foot. After about ten days in hospital, he was taken around the country in a caravan, and towards the end of December he was taken to a doctor in Portland. By this time the plaster spica was badly broken and was giving no fixation, and X-ray examination showed that the fracture was ununited and that absorption of the neck had occurred with displacement upwards of the greater trochanter on the head and neck. After this, he was admitted to the Hamilton Base Hospital. Under general anæsthesia, a left fibula graft was inserted into the head and neck of the right femur and a double plaster spica applied. Dr. Kneebone said that he proposed to remove the plaster in one month's time and see if the fracture had united. He thought that it still might be necessary to perform a subtrochanteric osteotomy.

DR. A. T. PARK opened the discussion by describing the X-ray appearances in the case. He considered that in the intermediate films there was very little change shown in the bone density on the affected side and that it would be interesting to see if union would still occur.

DR. R. SOUTHBY asked whether there was any possibility of a constitutional disease, such as syphilis, as an underlying cause of the fracture.

Dr. Kneebone replied that that had been thought of, but that the Wassermann test result was negative.

DR. RUSSELL HOWARD said that in similar cases in which treatment was by pinning, the patients did very well. However, in the present case there was the prolonged period without treatment to take into account. He considered that that was the correct treatment; if it was not satisfactory, then the area would have to be cleaned out and packed with bone chips. However, that should not be necessary.

DR. A. KELLY said he was interested in the accident causing the lesion and he wondered whether the case could really be one similar to a march fracture, due to prolonged strain or repeated minor injury.

### Vertebral Lesions.

Dr. Kneebone's second patient was a woman, aged fifty-one years, who, in mid October, 1952, had been confined to bed for six days with severe pain of sudden onset in the lower part of the back. She did not call a doctor, but, although her temperature was not taken, she felt sure that it was raised. After getting up, she consulted a doctor, as her back was still sore; she stated that he told her that she was suffering from influenza. In December, 1952, she consulted Dr. S. C. Fitzpatrick, as the back was still aching, and X-ray examination revealed a destructive lesion involving the inferior border of the second lumbar vertebra with narrowing of the adjacent disk. She was admitted to Hamilton Base Hospital and had since been nursed in a plaster bed turning case. The results of Wassermann and Mantoux tests were negative, as was the result of an agglutination test for brucellosis. Towards the end of February, 1953, X-ray examination showed evidence of organization and bony repair despite further destruction of the second lumbar vertebra and possible extension into the adjacent superior border of the third lumbar vertebra. No enlargement of either psoas shadow was demonstrable. A further X-ray examination in March showed comparatively rapid repair in progress, and the patient had been free of pain since being in the plaster bed. Dr. Kneebone said that he felt that the lesion was due to a blood-borne coccal infection, rather than that it was traumatic in origin.

DR. A. T. PARK wondered whether a disk lesion of traumatic origin might not have initiated the condition.

DR. A. KELLY wondered whether the condition was not another of the decalcifying lesions. It was hard to prove that the disease was of coccal origin—it might be due to localized hyperæmia. He thought that the treatment given was right, but wondered why mobility in a plaster cast in hyperextension had not been allowed.

In reply, Dr. Kneebone said that as it had been considered that the lesion was probably coccal in origin, as complete rest as possible had been aimed at.

Dr. Kneebone next showed a boy, aged fifteen years, who had been admitted to the Hamilton Base Hospital in February, 1952, with a history of injury to his back while wrestling at school six months previously. He had had severe pain for a few minutes, but it gradually decreased. He noticed that a lump developed in his back and gradually became more prominent, and that he experienced pain in his back when he sat erect on a piano stool. On examination of the boy, flexion and extension of the spine both caused some pain and kyphosis was present in the dorsi-lumbar region. The Mantoux test yielded a negative result, as did agglutination tests for typhoid fever and brucellosis. X-ray examination showed absorption of the anterior portion of the intervertebral disk between the first and second lumbar vertebræ with resultant kyphosis and a destructive lesion, surrounded by a little osteosclerosis on the anterior and inferior aspect of the body of the first lumbar vertebra. The chest showed no evidence of tuberculous infection, either in the lung fields or in the hilar glands. The patient was nursed in a plaster bed from his admission to hospital until October, 1952. At that time, X-ray examination suggested that the condition had improved and that some little bony regeneration had taken place. He was then allowed up for an increasing time each day, and he had been getting about for the last three months without any support. Exercises for the extensors of the spine had been carried out regularly, and his back seemed quite stable. Dr. Kneebone said that at first he thought that the condition was a coccal infection, but the question of such a condition as Schuermann's disease was now being considered.

DR. K. HALLAM said that no one's personal experience of cases such as the present one could be great. He thought that the lesion was an injured disk, with Schmorl's nodes on the posterior border of the affected vertebra. He explained that it had been stated that when that occurred, the condition was one of anterior rupture of the disk, due to shearing-off of the base anteriorly.

DR. C. R. WAIN asked if the patient could be treated like a subject of crush fracture—in other words, as an ambulatory patient.

Dr. Kneebone, in reply, explained that the patient had been originally treated as a subject of coccal infection; so full immobilization had been adhered to.

Dr. Kneebone's last patient was a boy, aged fifteen years, who was a bricklayer by trade. For some months he had had a pain in the back, low down and mainly to the left of the mid-line. In December, 1952, he had slipped on a rung of a ladder at work, while carrying a bucket of water, and struck his back on a projecting piece of wood. After that he could get up only with difficulty whenever he bent down. The next month he consulted a surgeon, who "pummelled" his back while he was in a stooping position with his hands resting on a table. After that his back felt easier, but he could not lift a heavy weight.

In February, 1953, after sitting in a chair, he found that he could not get up. He again went to Melbourne and had his back "pummelled", with relief of the difficulty in bending. At present, he stated that he was still unable to lift heavy weights, and that when he attempted to do so, an acute pain shot up his spine and he collapsed. That had happened several times, but at no time had he had pain in his legs.

At present, full flexion of his back was possible without pain, but lateral bending and extension of the spine caused discomfort at the level of the fourth lumbar vertebra. Straight leg raising caused no pain, and there were no abnormal motor or sensory signs in the leg. The X-ray appearances were considered typical of spondylolisthesis between the fourth and fifth lumbar vertebræ. Dr. Kneebone wondered about the treatment of the patient; he considered that there were three alternatives: (i) to encourage the patient to work, with X-ray control; (ii) to order a brace; (iii) to reduce the slip and stabilize the area with a graft.

DR. K. H. HALLAM considered that the boy had a "wobbly" vertebra, and that it had a degree of mobility far above the normal. It was for the surgeon to decide which was the correct line of treatment.

DR. LEONARD BALL said that although he was not an orthopædic surgeon, he thought that a spinal graft should be undertaken in such a case.

DR. W. R. ANGUS suggested, as an alternative, applying a plaster case for six months, and then, if there was still any slipping or symptoms, considering the question of a graft.

### Congenital Cardiac Conditions.

DR. I. S. EPSTEIN showed a series of patients with cardiac conditions. He said that he had two main reasons for showing the patients; the first was that he thought that they were of unusual interest, and the second was that they illustrated some interesting point of diagnosis or treatment.

The first patient was a man, aged fifty-two years, who had been well and active all his life. In 1940 he had been diagnosed by Dr. S. C. Fitzpatrick as having a transposition of viscera. He served in the army and continued in excellent health thereafter. On examination, he was a well-built man, with a blood pressure of 136 millimetres of mercury, systolic, and 76 millimetres, diastolic. His apex beat was difficult to define; cardiac dulness was detected to the right of the sternum, and heart sounds were maximal over that area. The liver dulness was present on the left side. X-ray examination of the chest showed the heart lying in the right hemithorax; the lung fields were clear. X-ray examination of the abdomen showed the liver on the left side and the stomach and pylorus lying to the left. An electrocardiogram showed an inverted *T* wave in lead I and leads II and III, with reversed leads. The *T* wave in lead I was upright, with normal leads.

DR. C. MCRAE said that the case was interesting and that the electrocardiogram was not the usual pattern seen with dextrocardia. He wondered whether the *T* wave inversion might be due to some left ventricular preponderance, but he had been unable to find any obvious reason for that.

DR. H. B. KAY thought that the tracing might be normal. He noted that the *P* waves, as well, were not correct for dextrocardia.

DR. S. C. FITZPATRICK said that he had warned the patient when he went into the army that he should let them know what was wrong with him, so that no surgical mistakes would be made.

Dr. Epstein's next three patients were all presented as having coarctation of the aorta. The first was a girl of six years. A murmur in her heart had been first noticed at the age of twelve months. Her general health had been satisfactory until six months before the time of the meeting, when she developed a respiratory tract infection, with persistent cough and general malaise. Two small attacks of hæmoptysis precipitated her admission to hospital. On examination, she was a well-developed child, with a good colour. Her apex beat was in the fifth left intercostal space, four inches from the mid-sternal line. A generalized harsh systolic bruit was heard, maximal at the base over the aortic area, conducted up to the neck and associated with a definite palpable thrill. No diastolic murmur was audible. Her femoral pulses were not palpable. The brachial blood pressure was 148 millimetres of mercury, systolic, and 76 millimetres, diastolic, and the femoral blood pressure could not be recorded. There was no evidence of collateral circulation on clinical examination. The diagnosis was made of coarctation of the aorta, with an associated congenital cardiac defect. X-ray examination of the chest showed some widening of the left ventricle, but it was still within normal limits. The aortic knob was not prominent. No definite notching was demonstrated. The electrocardiogram showed evidence of a left ventricular enlargement pattern. The patient was referred to Dr. H. B. Kay, who arranged her admission to the Alfred Hospital cardiological unit, and four months before the time of the meeting, Dr. C. J. Officer Brown had excised a coarctation of her aorta. She had an uneventful convalescence, was discharged from hospital ten days later and had remained well since. At present, her femoral pulses were easily palpable and normal in timing. Her blood pressure in the brachial artery was 110 millimetres of mercury, systolic, and 80 millimetres, diastolic, and in the femoral artery 120 millimetres of mercury, systolic, and 70 millimetres, diastolic. Her apex beat was in the fifth left intercostal space, four inches from the mid-sternal line. A generalized systolic bruit was audible, maximal over the base of the heart, conducted up to the neck and associated with a systolic thrill. Dr. Epstein said that it had been concluded that she had an associated congenital aortic stenosis, and Dr. Officer Brown considered that if, in the future, it appeared to be significant, it might be possible to perform valvotomy.

The second patient was a boy, also aged six years, who, four years previously, after a throat infection, had developed involuntary twitching movements and restlessness and was diagnosed as having chorea, for which he was kept at rest for six weeks. Since then, he had been reasonably well except that he had not grown as rapidly as his siblings and he suffered from repeated attacks of epistaxis. On examination, he was found to be a well-nourished but undersized lad, with no cyanosis or clubbing of the fingers. The apex beat was difficult to define, and a soft systolic bruit, maximal in the second left intercostal space, was evident. No thrill was noted. The blood pressure in the left arm was 130 millimetres of mercury, systolic, and 94 millimetres, diastolic, and in the right arm 160 millimetres of mercury, systolic, and 98 millimetres, diastolic. In the legs it was not recordable. Femoral pulses were not palpable, and no palpable superficial collateral arteries were noted. He had also been diagnosed as having coarctation of the aorta.

The third patient in the series was a married woman, aged twenty-two years, who had had two operations on her nose at the age of six and eight years, and chickenpox and measles as a child, but otherwise no serious illnesses. When aged seventeen years, she had applied for appointment as a trainee nurse at Saint Vincent's Hospital. She was advised against commencing training because "one valve of the heart was smaller than normal". She had never been conscious of any limitation of exercise tolerance. She was referred by Dr. M. C. Piercy for an opinion about her cardiac condition in relationship to pregnancy. On examination, she was a well-developed woman, of normal colour. The apex beat was in the fifth left intercostal space, four inches from the mid-sternal line. A generalized systolic bruit was audible, maximal at the base, where there was an associated, easily palpable, systolic thrill, conducted up to the neck. The aortic second sound diminished in intensity. Both radial impulses were difficult to palpate, but femoral pulses were impalpable. Her blood pressure was 113 millimetres of mercury, systolic, and 76 millimetres, diastolic, in the arms and unreadable in the legs. The X-ray screening examination of the chest showed the left ventricle on the upper limit of normal and dilatation of the ascending part of the aorta with a prominent aortic knob. No pulmonary congestion was noted. The electrocardiogram showed an inverted *T* wave in lead III; otherwise it was within normal limits. She was diagnosed as having congenital aortic stenosis and coarctation of the aorta.

DR. H. B. KAY said that, in his opinion, patients with coarctation did well if operated on early, but the problem of aortic stenosis was less certain. Symptoms occurred only when the area of the aortic valve opening was reduced to 25%. To distinguish an aortic from a subaortic stenosis, the presence of a secondary aortic sound and a difference in the pulse wave were important. Dr. Kay said that he would be interested to hear what others had to say about the group of patients, but he felt that they might be best left alone.

DR. C. J. OFFICER BROWN said that he had operated on 30 patients suffering from coarctation. In one case the condition was inoperable, as the whole of the descending aorta was narrowed. He had not used aorta grafts, as he had not needed them so far. Two of the patients had died: one died as the indirect result of a torn medial intercostal artery, and the other developed septicæmia on the tenth day (due to a resistant *Staphylococcus aureus*) and died of endarteritis. Dr. Officer Brown said that at first he had considered that the best time to operate was after the age of fifteen years and before the age of twenty. However, he had operated on a child of four years and on an adult of thirty-five years. Experimental work on animals, with interrupted silk sutures, suggested that the age of operation could be younger than fifteen years. That did not hold, however, with uninterrupted sutures. He now considered that any age from four years onwards was satisfactory. With regard to aortic stenosis, that had not yet been satisfactorily

operated on, but new techniques suggested that the operation might soon be possible—particularly in cases of rheumatic aortic stenosis.

DR. M. L. POWELL said that at the Children's Hospital there had been about 15 patients with coarctation, and, as yet, only one had had combined aortic stenosis and regurgitation. With regard to aortic stenosis alone, there were at present at the hospital some eight subjects—all fairly healthy children—and more than half the diagnoses had been proved by angiocardiography, in which the post-stenotic dilatation was the striking feature. Referring to the boy in Dr. Epstein's series who had not yet had his coarctation operated on, Dr. Powell said that there appeared to be an element of continuity in the bruit. Dr. Paul Wood might have said that that was due to a patent *ductus arteriosus*, but Dr. Powell thought it was more likely to be due to the coarctation itself.

DR. H. G. HILLER said that, in his opinion, the boy under discussion had a venous hum, as well as a coarctation. The lesion was very common in children, and, as was usual, the continuous murmur was best heard supraclavicularly and could be varied and even lost as a result of movement of the neck.

DR. RUSSELL HOWARD said that he wished to discuss the operative age for coarctation. Gross stated that he would not operate on patients aged less than eight years, unless there were pronounced symptoms. He, himself, had recently operated on two patients aged ten years, and the result had been entirely satisfactory. He wondered whether, if the operation was performed much earlier, the coarctation might not have a chance of reforming before the patient reached adult life.

DR. R. SOUTHBY thanked Dr. Epstein for his warning to feel for the femoral pulses in children failing to thrive. He asked whether any of the patients under discussion had had aching of the legs.

In reply, Dr. Epstein said that none had had aching of the legs.

DR. S. C. FITZPATRICK asked what was the earliest age at which notching of the ribs might be manifest.

DR. K. H. HALLAM considered that it all depended on when the intercostal vessels dilated to a sufficient extent.

DR. H. G. HILLER said that at the Children's Hospital the earliest case of notching they had had was in a child six years old.

DR. H. B. KAY said they had seen it at the Alfred Hospital in patients as young as four years.

DR. C. J. MCRAE wished to stress the importance in minor degrees of coarctation of the delay in occurrence of the femoral pulses. He considered that that was a really useful sign.

Dr. Epstein then showed a patient with pure congenital aortic stenosis, a young man of twenty-five years, who, at the age of twelve years, had been told that he had "a weak valve in the heart" and was advised to avoid heavy lifting and the like. He was not aware of any subjective limitation of exercise ability. Over the last few months, his heart had been beating harder than normal, he had lacked energy, and sustained physical exertion had caused a pain over the xiphisternum of gradual onset and offset. He had experienced a similar pain after meals, which he ascribed to indigestion. During that time, he had been under considerable nervous and emotional strain. There was no history suggestive of rheumatic fever. On examination, he was a well-developed man, with no cyanosis, and his apex beat was in the fifth left intercostal space, four inches from the mid-sternal line. A generalized systolic bruit was audible, maximal in the second and third left intercostal spaces, where there was a distinct blowing diastolic bruit. A systolic thrill was palpable at the base of the heart and conducted up to the neck. His femoral arteries were normal. The electrocardiogram showed a left-sided graph, and X-ray examination of the chest showed some dilatation of the aorta; the heart size was within normal limits, and the lung fields were clear.

Dr. Epstein next presented a patient with a condition for diagnosis. The patient was a girl, aged twenty-two years, who had failed to develop normally after birth. She had not gained weight and was cyanosed, particularly after crying. An X-ray picture, taken at the age of five months, had revealed an enlarged heart. A variable degree of cyanosis had persisted and, although she had developed physically, her exercise tolerance had been so impaired that she had not been capable of more than slight exercise. On examination, she was a slightly overweight, round-shouldered girl, with slight cyanosis of lips and fingers and a mild degree of clubbing of fingers and toes. Her apex beat was in the fifth left intercostal space, four inches from the mid-sternal line. No murmurs were audible, but there was a split pulmonary second sound. The femoral arteries were normal. An X-ray examination of the chest showed enlargement of the heart, with a prominent pulmonary conus and slight pulmonary congestion. The electrocardiogram showed right ventricular preponderance and peaked *P* waves. She was considered to be suffering from congenital *morbus cordis*, with pulmonary hypertension and cyanosis.

DR. H. B. KAY considered that the case was one of increased pulmonary flow, possibly with pulmonary hypertension. A catheter study would be necessary to reach a definite diagnosis, but it might well be a case of Eisenmenger's complex.

DR. M. POWELL said that the case typified the mildly cyanotic condition, with slight dyspnœa and congested lung fields, and was, therefore, not operable.

### Auricular Fibrillation.

Dr. Epstein finally presented three patients suffering from auricular fibrillation—in one case associated with mitral stenosis and thyrotoxicosis and in the other two of uncertain ætiology. All three had been treated with quinidine, with good results and return to normal rhythm in two cases, but with no effect on the rhythm in the third case.

DR. C. MCRAE said that there was certainly a group of young people who developed fibrillation for no apparent cause. He agreed that it was always worth trying quinidine with them, but, in his experience, it did not often work and then the patient's condition had to be controlled with digitalis.

DR. M. POWELL asked what was the maximum dose used in the cases under discussion.

In reply, Dr. Epstein said that up to 15 grains, given two hourly, for four doses, had been tried.

DR. C. R. WAIN inquired about the risks of quinidine treatment.

In reply, Dr. Epstein said that the main risk was that of embolism. He thought that perhaps anticoagulant therapy might lessen that risk.

DR. H. B. KAY said that he always used anticoagulant therapy, as he had been unlucky enough to have a case in which embolism occurred.

DR. W. R. ANGUS said that his experience with quinidine had been unsatisfactory—of the first four patients he had seen it used on, three had died. He wondered how safe it was. He, himself, had had three attacks of fibrillation which he had disregarded, and on each occasion his heart had reverted to normal rhythm.

DR. H. C. MALING asked about the possibility of septic foci as a cause of fibrillation.

In reply, Dr. Epstein said that in one of his cases, at least, it might have been a factor.

### Thoraco-Abdominal Conditions in Childhood.

In the evening Dr. Russell Howard read a paper on "Some Thoraco-Abdominal Conditions in Childhood". The paper was illustrated with lantern slides.

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## VICTORIAN BRANCH NEWS.

### Section of Preventive Medicine.

A MEETING of the Section of Preventive Medicine of the Victorian Branch of the British Medical Association will be held in the Medical Society Hall, 426 Albert Street, East Melbourne, on Thursday, July 9, 1953, at 4.30 p.m. Mr. F. N. Ratcliffe, Officer-in-Charge, Wild Life Survey Section, Commonwealth Scientific and Industrial Research Organization, Canberra, will give an address entitled "Myxomatosis: Recent Developments and Prospects". Dame Jean Connor (Dr. Jean Macnamara) will open the discussion and will be followed by Sir Macfarlane Burnet and others. All members of the Branch are invited to be present.

# Out of the Past.

*In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.*

## SPECIAL HOSPITALS.[1]

[*Australian Medical Gazette*, November, 1870.]

A CORRESPONDENT of the medical Times and Gazette who deplores the demoralizing tendency and injurious influence of these institutions on the members of the profession states that:

"Special hospitals and dispensaries are usually got up by young men with great ambition, no money, and often little or no professional experience, who, by advertising their name and address in connection with an institution hope to reach the drawing room through the kitchen."

# Correspondence.

## A COLLEGE OF GENERAL PRACTITIONERS.

SIR: Proposals to form regional faculties of the College of General Practitioners should not be dismissed without mature consideration. These regional faculties are to be established, if possible, in association with undergraduate and post-graduate medical schools, and thus their function is to be essentially educational (*vide British Medical Journal*, March 28, 1953).

The Australasian Colleges of Physicians and Surgeons and the several specialist groups have performed an admirable educational function. Undoubtedly they have raised the standard of specialist practice; particularly has their influence increased the facilities for post-graduate specialist studies. The road to specialism is so well sign-posted and made so smooth that young graduates may find the path unduly attractive. Herein lies a danger to the quality of general practice.

The medical requirements of a dispersed population need special study, and in this country they present a national problem. In America rural health services have received intensive study by varied authorities, medical and lay, governmental, university and industrial. In Australia very little integrated work has been done in this direction. Perhaps a College of General Practitioners could provide a rallying point for the many interested in these vital matters.

Yours, etc.,

H. M. SAXBY.

69 East Street,
Ipswich,
Queensland.
June 9, 1953.

## HORNER'S SYNDROME FOLLOWING RIB INJURY.

SIR: This case ought I think be placed on record on account of its rarity and interest. The literature as far as I have searched does not show a similar case.

Miss M.M., aged twenty-four years, suffered fractures of left second, third, fourth, seventh and eighth ribs in a motor injury. She reported to a casualty department within one hour of the injury. Examination showed, *inter alia*, a classic left Horner's syndrome. The ptosis was especially marked, and the pupillary narrowing was notable. The pupillary reflexes were barely perceptible.

After three weeks the pupil began to enlarge in diameter, and today (ten weeks after injury) there is still notable difference in pupillary diameters, although pupillary reactions appear normal. There is no ptosis.

It is reasonably surmised that the fractured third rib was accompanied by a tense hæmatoma which involved the upper part of the sympathetic trunk on the left side.

The left side of face no longer feels uncomfortably warm, and the patient feels no disability, while visual acuity is normal.

Yours, etc.,

JOHN R. S. LAHZ.

Wickham Terrace,
Brisbane,
May 29, 1953.

## GARTNER'S DUCT.

SIR: May I submit through your columns a plea for writers, readers and printers to realize that the spelling of the headline of this note is correct and not an error of omission of the *umlaut*.

Herman Treschow Gartner, a Dane (1785-1827), rediscovered in the sow, in 1822, the vestigial Wolffian ducts, which had already been seen by Marcello Malpighi in 1681 in the calf.

According to Robert Meyer, the first descriptions of Gartner's ducts in the human female were published in 1833 by Baudeloque and Dugés and in 1848 by Meckel, in an hermaphrodite.

The name "Gärtner" is used in a different eponym. Gärtner dysentery, Gärtner's bacillus (*Salmonella enteritidis*) are named after August Gärtner, a German bacteriologist (1848-1934).

Yours, etc.,

H. F. BETTINGER.

Department of Pathology,
The Women's Hospital,
Melbourne, N.3.
June 9, 1953.

## TRAUMATIC VAGINAL HÆMORRHAGE.

SIR: I was interested in the article on "Traumatic Vaginal Hæmorrhage" by T. I. Cope in your issue of June 6.

Several years ago while practising in a Victorian holiday resort I was summoned to a large and popular guest house, where I found a young woman lying in bed in an absolute welter of blood. It transpired that she was a bride of some eighteen hours. Coitus had been attempted the night before, and temporarily abandoned on account of the discomfort caused. However, on the morning in question, a determined attempt had been made, followed almost immediately after full penetration by torrential hæmorrhage.

I removed her to my surgery, blankets and all, and proceeded to look for the source of the bleeding. After clearing the vulva of blood clot it became apparent that the trouble was higher up. A very large quantity of blood and clot was evacuated from the vagina, when, by the light of a tonsillectomy head lamp, the injury became apparent—a large rent through the left fornix into the left broad ligament; and both ends of a torn uterine artery could be seen pumping steadily.

The vagina was hastily plugged, a colleague summoned, and under general anæsthesia the ends of the artery caught with long Howard Kelly forceps and sutured with the aid of a tonsillectomy needle. The patient, although rather shocked, made a rapid and uneventful recovery.

Comic relief was provided by the bridegroom, who, when he came to settle the account, added a request not to "dig too deep".

Yours, etc.,

C. W. HAMMOND.

Maclean,
Clarence River,
New South Wales.
June 10, 1953.

## HYPERPLASTIC CYSTIC DISEASE OF THE BREAST.

SIR: I am indebted to Dr. G. Gall for his interesting comments (M. J. AUSTRALIA, May 30, 1953) on my recent article on hyperplastic cystic disease. He refers to the belief that this condition is premalignant and suggests that a follow-up of the 199 patients would be of value in settling this question.

Nothing would give me more pleasure were I convinced that the effort was justifiable. Such studies, however, have

[1] From the original in the Mitchell Library, Sydney.

been already conducted by a host of other workers in this field who have access to the large numbers of patients necessary to qualify their work for statistical significance.

Without going into detail it may be stated that, despite an immense amount of research into this subject, the issue is still in doubt. Dr. Gall may be interested to know that I put this same question to Sir Gordon Gordon-Taylor during his visit to Sydney last September. His reply consisted of only two words, namely: "Prophylactic against!"

Dr. Gall also harbours doubts about the infallibility of biopsy and quotes two cases with woeful results. It is useless to deny that such mistakes occur occasionally. Someone has said "biopsy depends on the biopsist". It is my own view that the method is sound, that occasional upsets are the exception and not the rule, and that when they occur they are due to lapses by the surgeon rather than by the pathologist.

In this connexion it is of interest to recall that local massage has been shown to hasten the spread of mammary carcinoma in mice. For this reason a well-conducted biopsy is probably better management than long drawn-out and repeated palpation in doubtful cases.

Finally, Dr. Gall gives details of a patient who developed secondaries in the spine after expert surgery at an early stage, and proffers the view that the operation may have hastened the spread of cancer cells. Most surgeons have had this unhappy experience upon occasion, and indeed a somewhat similar case of my own has been recently accepted for publication in this journal.

If radical operation were actually harmful and not beneficial, it would have been abandoned years ago. The facts are that this is the treatment of choice, backed by impressive statistics, in nearly all the world's important surgical clinics. There is little doubt that in the case described by Dr. Gall the metastases had safely arrived in the bones by courtesy of the blood-stream prior to operation.

Yours, etc.,

135 Macquarie Street,
Sydney,
June 11, 1953.

JAMES MACRAE YEATES.

# Naval, Military and Air Force.

## APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 33, of May 28, 1953.

### CITIZEN NAVAL FORCES OF THE COMMONWEALTH.

*Royal Australian Naval Reserve.*

*Transfer to Retired List.*—Surgeon Commander Malcolm James Lees Stening is transferred to the Retired List, dated 19th March, 1953.

### AUSTRALIAN MILITARY FORCES.

**Citizen Military Forces.**

*Northern Command: First Military District.*

*Royal Australian Army Medical Corps (Medical).*—The provisional rank of 1/39109 Captain G. J. McCafferty is confirmed. 1/46756 Honorary Captain G. Borzi is appointed from the Reserve of Officers, and to be Captain (provisionally), 7th March, 1953. 1/10563 Captain A. J. Mooney is appointed from the Reserve of Officers, 27th March, 1953. 1/39109 Captain G. J. McCafferty is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (1st Military District), 26th March, 1953.

*Eastern Command: Second Military District.*

*Royal Australian Army Medical Corps (Medical).*—2/127804 Major K. M. McNamee is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (2nd Military District), 26th February, 1953. 2/121942 Captain (provisionally) J. H. Lancken relinquishes the provisional rank of Captain and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (2nd Military District) in the honorary rank of Captain, 31st January, 1953. To be Captain (provisionally), 7th April, 1953: 2/127884 Graham Beresford Smith.

**DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED MAY 23, 1953.[1]**

| Disease. | New South Wales. | Victoria. | Queensland. | South Australia. | Western Australia. | Tasmania. | Northern Territory. | Australian Capital Territory. | Australia. |
|---|---|---|---|---|---|---|---|---|---|
| Acute Rheumatism | .. | 3(3) | .. | .. | .. | .. | .. | .. | 3 |
| Amœbiasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ancylostomiasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Anthrax | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Bilharziasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Brucellosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Cholera | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Chorea (St. Vitus) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Dengue | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Diarrhœa (Infantile) | 3(1) | 2(2) | 7(6) | .. | .. | .. | 1 | .. | 13 |
| Diphtheria | 16(4) | 3(1) | 4(3) | .. | 5(4) | .. | .. | .. | 28 |
| Dysentery (Bacillary) | .. | 2(2) | .. | 1(1) | .. | .. | .. | .. | 3 |
| Encephalitis | .. | 1(1) | .. | 2(1) | .. | .. | .. | .. | 3 |
| Filariasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Homologous Serum Jaundice | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Hydatid | .. | 1 | .. | .. | .. | .. | .. | .. | 1 |
| Infective Hepatitis | .. | 7(3) | .. | .. | 5(4) | .. | 1 | .. | 13 |
| Lead Poisoning | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Leprosy | .. | .. | .. | .. | .. | .. | 1 | .. | 1 |
| Leptospirosis | .. | .. | 2 | .. | .. | .. | .. | .. | 2 |
| Malaria | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Meningococcal Infection | 2 | 3(1) | 1 | .. | .. | .. | .. | .. | 6 |
| Ophthalmia | .. | .. | .. | .. | 5 | .. | .. | .. | 5 |
| Ornithosis | .. | 2(2) | .. | .. | .. | .. | .. | .. | 2 |
| Paratyphoid | 1 | .. | .. | .. | .. | .. | .. | .. | 1 |
| Plague | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Poliomyelitis | 10(9) | 4 | 8(1) | 12(11) | 1(1) | .. | .. | .. | 35 |
| Puerperal Fever | .. | .. | 3(3) | .. | .. | .. | .. | .. | 3 |
| Rubella | .. | 24(11) | .. | .. | 4(1) | .. | 1 | .. | 29 |
| Salmonella Infection | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Scarlet Fever | 11(5) | 73(49) | .. | 2(1) | 1(1) | 1(1) | .. | .. | 88 |
| Smallpox | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tetanus | .. | 1 | .. | .. | 1 | .. | .. | .. | 2 |
| Trachoma | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Trichinosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tuberculosis | 28(19) | 18(12) | 12(1) | 10(8) | 4(4) | 5(3) | .. | .. | 77 |
| Typhoid Fever | 1 | .. | .. | .. | .. | .. | .. | .. | 1 |
| Typhus (Flea-, Mite- and Tick-borne) | .. | .. | 2 | .. | .. | .. | .. | .. | 2 |
| Typhus (Louse-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Yellow Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |

[1]Figures in parentheses are those for the metropolitan area.

*Southern Command: Third Military District.*

*Royal Australian Army Medical Corps (Medical).*—The provisional rank of 3/97030 Captain P. C. B. Bradley is confirmed. To be Major, 16th April, 1953: 3/97030 Captain P. C. B. Bradley.

*Western Command: Fifth Military District.*

*Royal Australian Army Medical Corps (Medical).*—5/26394 Captain (Honorary Major) H. J. Rowe ceases to be seconded for post-graduate studies in United Kingdom, 20th February, 1953. To be Captain (provisionally), 22nd April, 1953: 5/26521 Malcolm Chennell Smith.

*Tasmania Command: Sixth Military District.*

*Royal Australian Army Medical Corps (Medical): To be Captains (provisionally), 16th April,* 1953.—6/15412 Alan John Stubley and 6/15413 William Hugh Patterson.

**Reserve Citizen Military Forces.**

*Royal Australian Army Medical Corps.*

*1st Military District: To be Honorary Captains.*—Harold Alexander Bell Foxton and Westall David Smout, 6th April, 1953, Rogert William Percy, 1st May, 1953, and Alexander Boardman Shearer and John Henry Cameron, 4th May, 1953. The resignation of Honorary Captain M. S. Marshall of his commission is accepted, 13th April, 1953.

ROYAL AUSTRALIAN AIR FORCE.

*Permanent Air Force: Medical Branch.*

The following are appointed to short-service commissions on probation for a period of twelve months, with rank as indicated: (Flight Lieutenant) Lawrence Neville Walsh (039383), 14th April, 1953; (Pilot Officer) Lionel Thomas Cooper West (041923), 30th March, 1953.

Pilot Officer N. W. Williams (024203) is transferred from the Reserve and appointed to a short-service commission, on probation for a period of twelve months, 3rd March, 1953, with the rank of Flight Lieutenant.

## Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

**Lecture in Medical Statistics.**

THE Post-Graduate Committee in Medicine in the University of Sydney announces that Dr. Malcolm Whyte, Director of the Clinical Research Unit, Sydney Hospital, will address the Statistical Society of New South Wales on Thursday, July 23, 1953, on "Clinical Trials". Professor C. W. Emmens and Miss H. Newton Turner will contribute to the meeting, which will begin at 7.30 p.m. at the School of Public Health and Tropical Medicine, University Grounds. All visitors will be welcome to attend.

## Deaths.

THE following deaths have been announced:

HARDY.—Lowen Alexander Hardy, on May 26, 1953, in London.

RAY.—William Ray, on June 6, 1953, at Melbourne.

MACKNIGHT.—Conway Montgomery Macknight, on June 11, 1953, at Melbourne.

CHAPMAN.—Henry Thomas Chapman, on June 13, 1953, at Melbourne.

## Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Bloch, Bernard, M.B., Ch.B., 1945 (Univ. Witwatersrand), F.R.C.S. (England), 1952, 393 Darling Street, Balmain.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Ash, Douglas, M.B., B.S., 1953 (Univ. Sydney); Birch, Patricia Ormonde, M.B., B.S., 1953 (Univ. Sydney); Egan, Francis John, M.B., B.S., 1953 (Univ. Sydney); Flower, Willoughby, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Fuller, Lester Keith, M.B., B.S., 1953 (Univ. Sydney); Greer, Bernard Louis, M.B., B.S., 1953 (Univ. Sydney); Regan, William, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Roberts, Thomas Leslie, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Roper, Walter Geoffrey, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Spence, Barry Blackwood, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Stanbury, John Gregory, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Steel, Mark, M.B., B.S., 1953 (Univ. Sydney); Voloshin, Olga, provisional registration, M.B., B.S., 1953 (Univ. Sydney); Jefferis, Robert William, M.B., B.S., 1952 (Univ. Sydney); Kelly, Douglas Heron, M.B., B.S., 1950 (Univ. Sydney); Wilson, Dennis de Courcy, M.B., B.S., 1949 (Univ. Adelaide); Ravazdy, Stefan, M.D., 1943 (Univ. Szeged) (regional registration for Stroud region).

## Diary for the Month.

JULY 1.—Victorian Branch, B.M.A.: Clinical Meeting.
JULY 1.—Western Australian Branch, B.M.A.: Council Meeting.
JULY 3.—Queensland Branch, B.M.A.: General Meeting.
JULY 7.—New South Wales Branch, B.M.A.: Council Quarterly.
JULY 10.—Queensland Branch, B.M.A.: Council Meeting.
JULY 13.—Victorian Branch, B.M.A.: Finance Subcommittee.

## Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

*Victorian Branch* (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federal Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 178 North Terrace, Adelaide): All Contract Practice appointments in South Australia.

*Western Australian Branch* (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all Contract Practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

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